CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215888Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 22, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsule, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-6
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling (child resistant wallet and outer carton) received on April 21, 2022 for Vivjoa for their proposed Vivjoa-only dosage regimen.[a] The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling (child resistant wallet and outer carton) for Vivjoa for the proposed Vivjoa-only dosage regimen (Appendix A) to determine if they are acceptable from a medication error perspective. The revision is in response to our Information Request (IR) dated April 20, 2022.[b]

2 BACKGROUND

We previously requested the Applicant *"…increase the font size and bold the middle digits (product code) of the NDCs on both products."* [c]

[a] Cover Letter: Response to Information Request – Wallet and Carton Labeling for Vivjoa (NDA 215888). Durham (NC): Mycovia Pharmaceuticals, Inc.; 2022 APR 21. NDA 215888. Available at: \\CDSESUB1\evsprod\nda215888\0068\m1\us\cover.pdf.
[b] DiBernardo, G. FDA Communication: FDA Communication: NDA 215888-Vivjoa (oteseconazole)-Mycovia-DMEPA Labeling IR-C&C Sent to Applicant on 4/20/22. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 APR 20. NDA 215888. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806599da.
[c] Myers, D. Label and Labeling Review for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 16. RCM No.: 2022-1075-3.

3 CONCLUSION

The Applicant implemented our recommendation and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 21, 2022

Container label

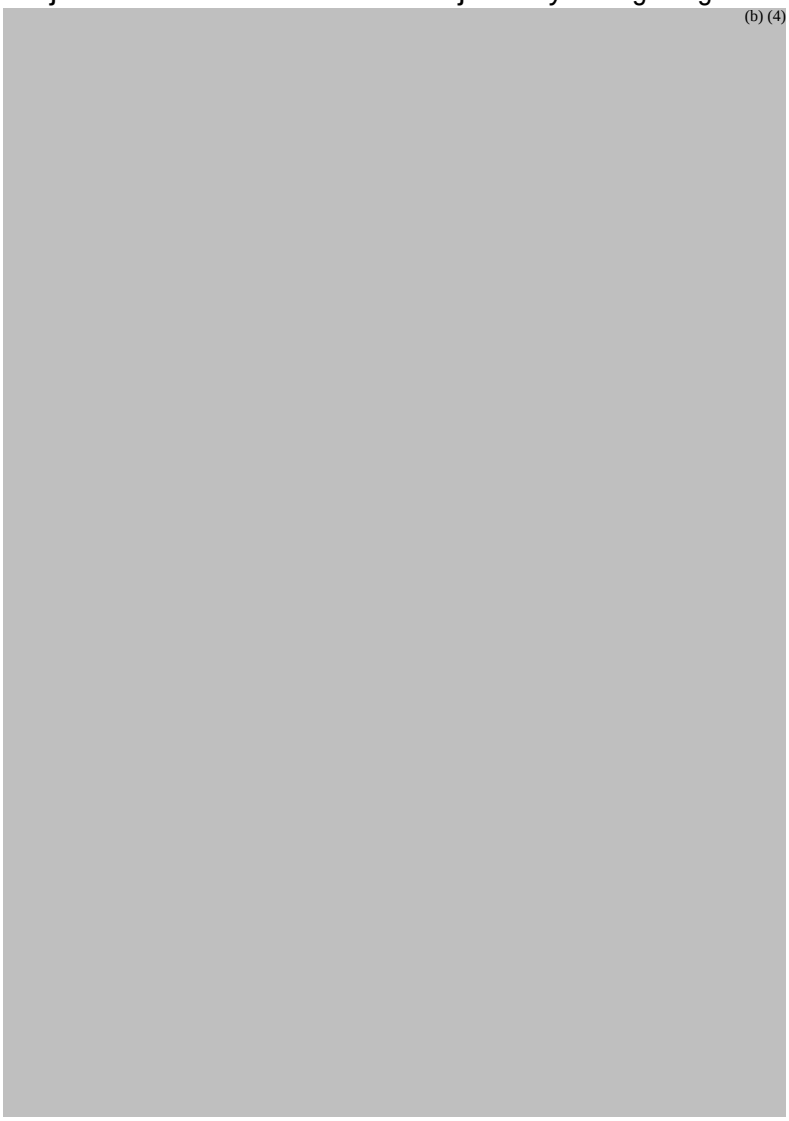
Vivjoa container label (blistercard) for Vivjoa-only dosage regimen

(b) (4)

Carton labeling

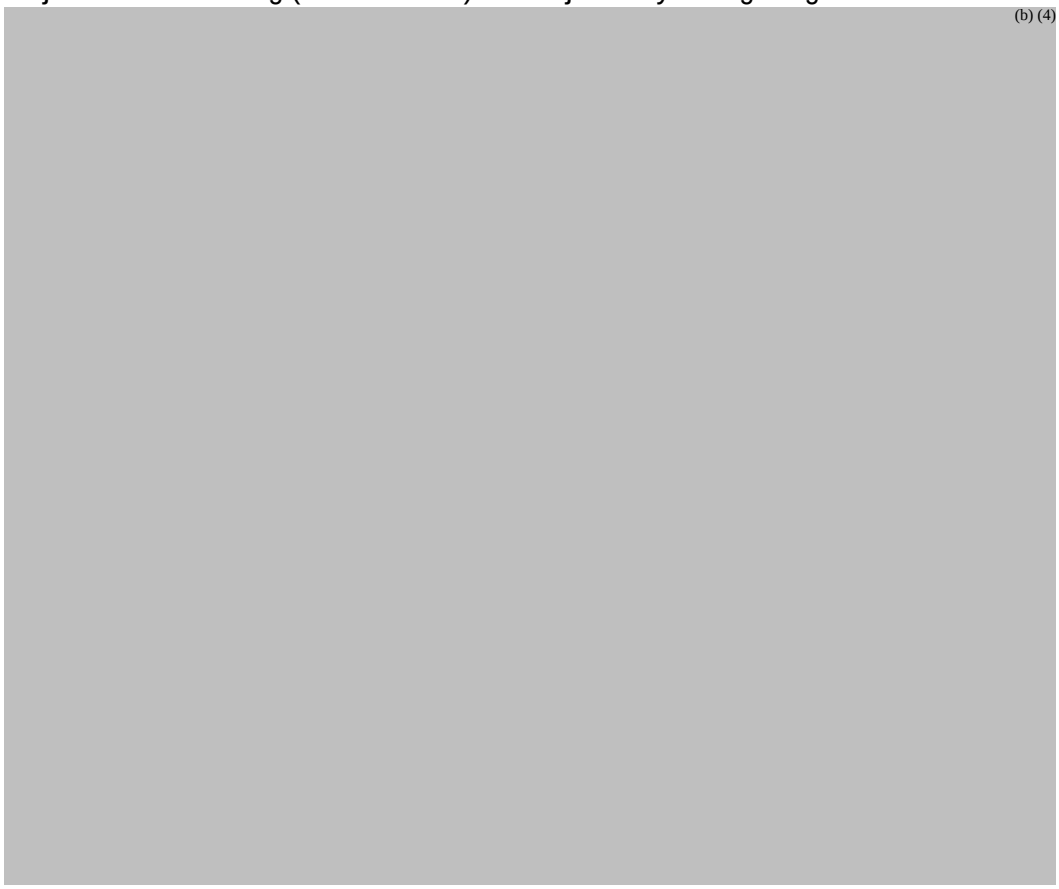
Vivjoa child resistant wallet for Vivjoa-only dosage regimen

(b) (4)



Vivjoa carton labeling (outer carton) for Vivjoa-only dosage regimen

(b) (4)



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/s/

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VALERIE S VAUGHAN
04/22/2022 12:58:07 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 15, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-5
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling (child resistant wallet and outer carton) received on April 15, 2022 for Vivjoa for their proposed fluconazole/VIVJOA dosage regimen. The Division of Anti-Infectives (DAI) requested that we review the revised carton labeling for Vivjoa for the proposed fluconazole/VIVJOA dosage regimen (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Myers, D. Label and Labeling Review for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 APR 11. RCM No.: 2021-1075-4.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 15, 2022

Carton labeling

Vivjoa child resistant wallet for fluconazole/VIVJOA dosage regimen

(b) (4)

Vivjoa carton labeling (outer carton) for fluconazole/VIVJOA dosage regimen

(b) (4)

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/s/

DEBORAH E MYERS
04/15/2022 01:04:30 PM

VALERIE S VAUGHAN
04/15/2022 01:22:51 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 11, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-4
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infectives (DAI) requested that DMEPA 1 review Mycovia's response to our previous IR, dated March 18, 2022, as well as their revised container label (blistercard), carton labeling (child resistant wallets and outer cartons), Prescribing Information (PI), and Patient Package Inserts (PPI) for Vivjoa (Appendix A) to determine if they are acceptable from a medication error perspective.

2 BACKGROUND

On March 25, 2022, Mycovia submitted their response[a] to our Information Request (IR) dated March 18, 2022. Additionally, along with their response to our IR dated March 18, 2022, Mycovia submitted their revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for the fluconazole/Vivjoa dosage regimen. The revisions are in response to

[a] Response to FDA Request for Information – Carton and Container Labeling for Vivjoa (NDA 215888). Durham (NC): Mycovia Pharmaceuticals, Inc.; 2022 MAR 25. NDA 215888. Available at: \\CDSESUB1\evsprod\nda215888\0065\m1\us\ir-resp-alt-dose-reg-carton-contain-lbl.pdf.

recommendations that we made during a previous label and labeling review.[b] Furthermore, Mycovia submitted their revised Prescribing Information (PI) and two Patient Package Inserts (PPIs), received on March 28, 2022.

3 DISCUSSION

We evaluated Mycovia's IR response, revised container labels, carton labeling, PI, and PPIs.

We find Mycovia's responses to the concerns outlined in our March 18, 2022 IR acceptable from a medication error perspective. Regarding Mycovia's risk mitigation plan to ensure differentiation of the Vivjoa-only and fluconazole/Vivjoa regimens throughout the entire medication use process, Mycovia agrees to work with their Electronic Health Record (EHR) integration partner to optimize the appearance of the two regimens in EHRs (i.e., when ordering, a prescriber will see "Vivjoa" and "fluconazole/Vivjoa" descriptors to aid in selection of the intended Vivjoa regimen). Additionally, Mycovia agrees to add clarifying details to reflect that a separate fluconazole prescription is required for the fluconazole/Vivjoa regimen given that fluconazole will not be co-packaged with Vivjoa. Furthermore, Mycovia clarified that no outpatient pharmacies outside of their Limited Pharmacy Network system will be able to order, dispense, or bill for Vivjoa, nor will Vivjoa be dispensed for inpatient use. From the postmarket perspective, Mycovia provided additional details on their plan to ensure the correct dosage regimen is identified in the postmarket reports they receive. Refer to Appendix B for additional details pertaining to our assessment of Mycovia's full IR response.

We note that Mycovia's responses to items 6 and 7 are in reference to additional information requested by our colleagues in DEPI/Drug Utilization. Thus, we defer to our DEPI/Drug Utilization colleagues to determine the acceptability of Mycovia's responses to items 6 and 7.

We find that Mycovia has taken reasonable steps to differentiate the two Vivjoa container labels and carton labeling to mitigate selection error through use of different background colors, NDCs, and a unique descriptor for the fluconazole/Vivjoa regimen container label and carton labeling. However, we note that the current text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (4) the PDP) on the outer carton labeling lacks prominence and may be overlooked. Since the proposed product will be dispensed in the individual outer carton, the prominence of the aforementioned text on the outer carton is important to differentiate the regimens, provide a reminder that fluconazole is prescribed separately, and reduce the risk of medication errors. Therefore, we recommend increasing the prominence of the statement on the outer carton labeling.

Additionally, we note that the dosage instructions on the container label and carton labeling intended for the fluconazole/Vivjoa regimen are aligned with the PI, as requested, and clearly denote that fluconazole is prescribed separately. We find that the revised PI incorporates all the requested FDA changes. Furthermore, we note that in the revised PI, Mycovia has updated Section 16 to include the NDC number for the fluconazole/VIVJOA dosage regimen container label and

[b] Myers, D. Label and Labeling Review Memo for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 16. RCM No.: 2021-1075-3.

carton labeling, as well as relevant information regarding the available dosage form and packaging presentation.

Mycovia agreed with the FDA's recommendation to supply separate PPIs for each of the respective Vivjoa regimens. The two PPIs incorporate the FDA recommendations to better distinguish between the two Vivjoa dosage regimens and minimize confusion or wrong dose errors that might occur if patients were to see both Vivjoa dosage regimens in a single PPI. Moreover, each PPI can be dispensed with its respective Vivjoa or fluconazole/Vivjoa dosage regimen container label and carton labeling.

Based on our overall evaluation of materials reviewed, we have no additional comments for Mycovia's Vivjoa risk mitigation plan, container labels, PI, or PPIs. However, as discussed above, we provide a recommendation in Section 5 to increase the prominence of the text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (4) (b) (4) the PDP) on the outer carton labeling.

4 CONCLUSION

The revised container label, Prescribing Information, two patient package inserts and Mycovia's Vivjoa risk mitigation plan are acceptable from a medication error perspective. However, we provide our recommendation in Section 5 to increase prominence to the current text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (6) (b) (6) the PDP) on the carton labeling (outer carton).

Additionally, we defer to our DEPI, Drug Utilization colleagues, to assess Mycovia's responses to IR items 6 and 7.

5 RECOMMENDATIONS FOR MYCOVIA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

As currently presented, the text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (4) the principal display panel (PDP)) on the outer carton labeling lacks prominence. We acknowledge that when the two products (VIVJOA-only dosage regimen and fluconazole*/VIVJOA dosage regimen) are displayed side-by-side, the difference in color (purple vs. green, respectively) may provide some differentiation. Yet, we are concerned that the text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" on the outer carton labeling may be overlooked. This statement is important to differentiate the regimens, provide a reminder that fluconazole is prescribed separately, and reduce the risk of medication errors. Therefore, we recommend that you revise the font color of the text to black, relocate this text to the left side of the PDP, and box this text, to increase prominence of the statement. For example:

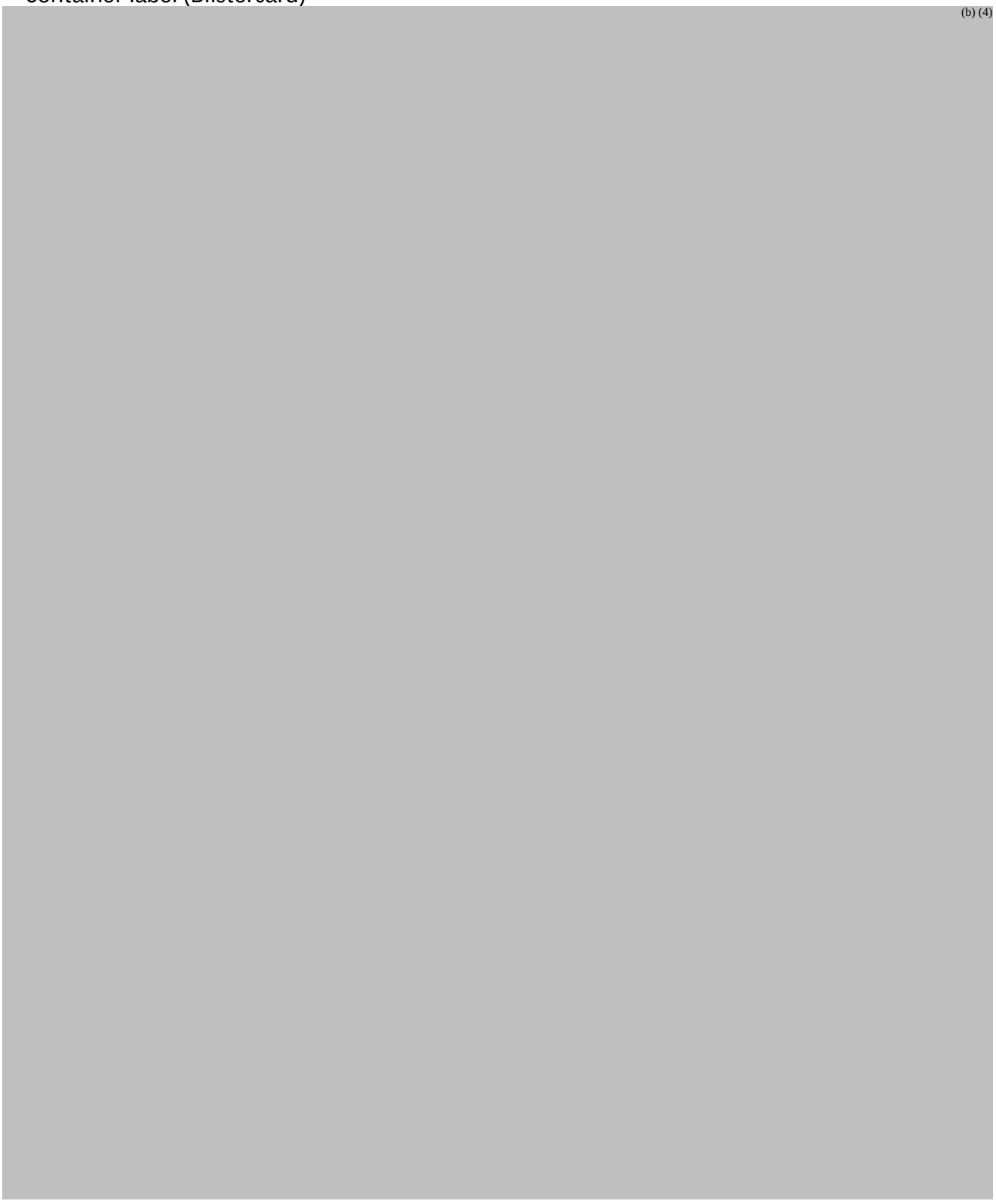
fluconazole*/VIVJOA dosage regimen
*fluconazole is prescribed separately

Additionally, to provide consistency and alignment between the revised carton labeling and the currently proposed child resistant wallet, we recommend that you also box the above text on the child resistant wallet.

APPENDIX A. IMAGES OF LABEL AND LABELING REVIEWED

Label and Labeling for fluconazole/VIVJOA dosage regimen – received on March 25, 2022

Container label (Blistercard)



fluconazole/VIVJOA dosage regimen – Carton labeling (outer carton)

(b) (4)

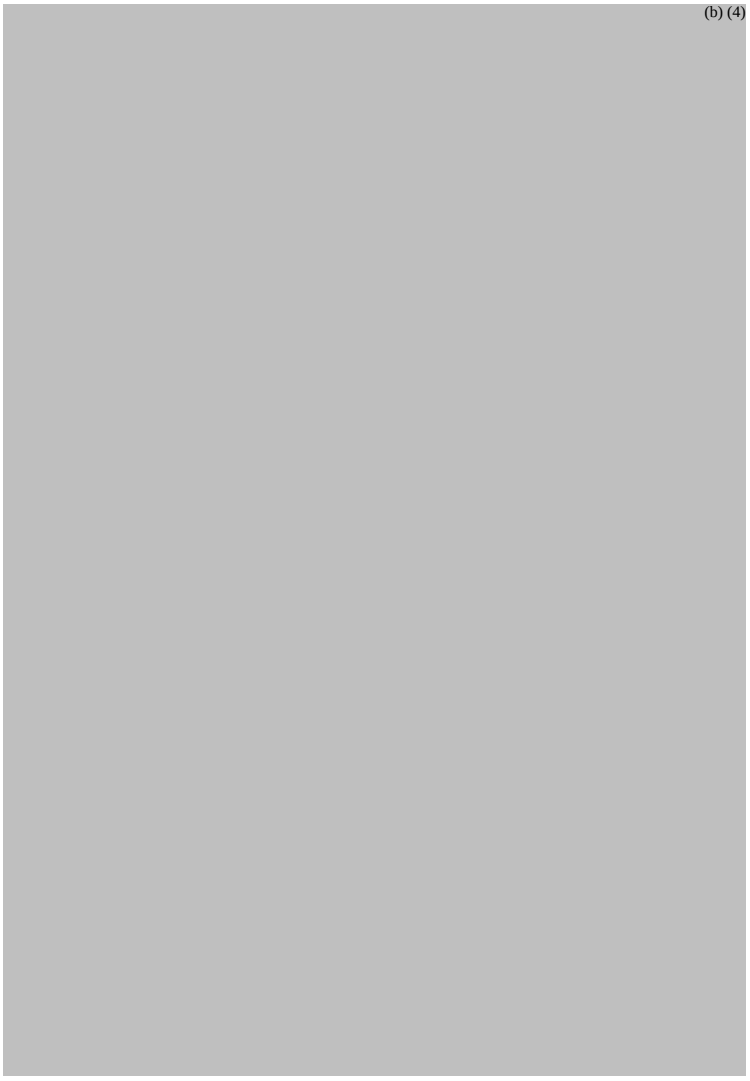
Label and Labeling for VIVJOA-only dosage regimen – received on January 25, 2022

Container label (Blistercard)

(b) (4)

Child resistant wallet

(b) (4)



Carton labeling (outer carton)

Prescribing Information (Image not shown) received on March 28, 2022, available at: \\CDSESUB1\evsprod\nda215888\0066\m1\us\draft-labeling-text-clean.pdf.

Patient Package Insert for Vivjoa-only regimen (Image not shown) received on March 28, 2022, available at: \\CDSESUB1\evsprod\nda215888\0066\m1\us\draft-patient-label-vivjoa-clean.pdf.

Patient Package Insert for fluconazole/Vivjoa regimen (Image not shown) received on March 28, 2022, available at: \\CDSESUB1\evsprod\nda215888\0066\m1\us\draft-patient-label-fluconazole-vivjoa-clean.pdf.

APPENDIX B. ANALYSIS OF MYCOVIA'S INFORMATION REQUEST RESPONSE RECEIVED MARCH 22, 2022

Our analysis of Mycovia's responses, dated March 25, 2022, to the concerns outlined in our Information Request (IR) dated March 18, 2022 is outlined below:

- We considered Mycovia's response 1a, regarding our concern involving product listing being truncated in the Electronic Health Record (EHR) and computerized physician order entry (CPOE) systems and thus, the differentiation may not be picked up by prescribers. Mycovia states that "*EHRs do not truncate terms or words to minimize confusion and potential prescribing errors (with exception for units of measure such as mg instead of "milligrams").*" Additionally, Mycovia states that "*Optimizing the EHR and making the descriptions of the two regimens (Vivjoa, fluconazole/Vivjoa) as clear as possible provides a path to minimize potential prescribing errors.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1b, regarding our concern that within Mycovia's EHR example, the proposed fluconazole/Vivjoa dosage regimen description does not clarify that fluconazole needs to be prescribed separately. Additionally, we recommend clarifying in the EHR that fluconazole is not co-packaged with Vivjoa. Mycovia states that they "*agree and will work with our EHR integration partner to add clarifying details for the "fluconazole/VIVJOA regimen" to reflect that fluconazole requires a separate prescription and is not co-package with Vivjoa.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1c, regarding our concern whether *all* prescriptions will be prescribed via EHR and if this is the case, how this will be enforced (i.e., how to ensure that Healthcare Professionals (HCPs) will not provide patients with paper prescriptions). Mycovia states that "*HCPs have the option to prescribe any non-controlled drugs via EHR, paper/faxed, or by phone…it is anticipated that the vast majority of prescriptions will be prescribed via EHR as this follows national prescribing trends…Additionally, the Mycovia sales force will provide education and onboarding to target HCP practices on where to find Vivjoa within the EHR.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1e, regarding our concern whether other pharmacies outside of the limited pharmacy network would be able to order and dispense Vivjoa (for instance, if a paper prescription were brought into another pharmacy by a patient). Additionally, whether the prescriptions would be verified at both the Integrated Intake Pharmacy level and the network pharmacy level (as opposed to the Integrated Intake Pharmacy level only), to ensure that the correct product is provided to the patient. Mycovia states that "*Outpatient pharmacies outside of the Limited Pharmacy Network will not be able to order and dispense Vivjoa. For example, if a patient brings in a paper prescription to a pharmacy outside of the Limited Pharmacy Network, the pharmacy will not be able to order, dispense or bill for Vivjoa.*" Additionally, "*Prescriptions will be verified by both the Integrated Intake Pharmacy and the Limited Pharmacy Network.*" We find

Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.

- We considered Mycovia's response 1f, regarding our concern that the inadvertent omission of or overlooking the descriptive text (b) (4) on a prescription by the provider/pharmacist, respectively, could lead to the wrong product (i.e., Vivjoa only regimen) being dispensed (along with fluconazole). Mycovia states that *"The Integrated Intake Pharmacy will have multiple touchpoints with patients. During these touchpoints, the pharmacy will provide medication counseling to help ensure patients take their prescriptions as appropriate and prescribed. The Integrated Intake Pharmacy will employ a series of questions to help identify if the patient is currently taking or planning on taking fluconazole to identify potential prescribing errors or patient confusion on how to take the prescribed regimen. If a prescribing error is identified, the pharmacy process will be paused and Vivjoa will not be dispensed until the prescriber can be contacted, the prescription corrected, and the patient counseled appropriately."* We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1g, regarding our concern that from an inpatient perspective, it is unclear how the prescription for Vivjoa would enter your proposed Integrated Intake Pharmacy and Limited Pharmacy Network system. Mycovia states that "*Due to the nature of the disease (RVVC) and length of Vivjoa treatment (12-weeks of therapy), we anticipate approximately 99% of Vivjoa prescriptions will be dispensed in the outpatient setting. Marketing and sales force initiatives are targeted at the outpatient/clinic level with no promotional initiatives for inpatient/hospitals. There will be no inpatient hospital dispensing within our Limited Pharmacy Network.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1i, regarding our concern that patient instruction printouts that would be provided by the pharmacy based on the compendia (i.e., Micromedex). Additionally, we note that the referenced "print outs" are not regulated by the Agency. Mycovia states that "*The Limited Pharmacy Network will be trained clinically on Vivjoa and will provide the Vivjoa prescribing information (PI) and the patient package insert (PPI) upon dispensing.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1j, regarding our concern as to how Mycovia plans to target all potential healthcare providers that will prescribe and/or dispense Vivjoa to educate them on prescribing regimens and how to prescribe. Mycovia states that they are *"…not targeting all potential HCPs. Mycovia sales and marketing efforts will promote Vivjoa to HCPs on our target list. Targeted HCPs will be reached either directly through personal promotion, i.e., Mycovia sales representatives and/or through Mycovia non-personal promotional channels such as digital marketing campaigns. A variety of promotional and educational materials are being developed that include the proper administration usage per the PI for the two dosing regimens: Vivjoa and Fluconazole/Vivjoa."* We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.

- We considered Mycovia's response 1k, regarding our concern that outside of HCP education, how does Mycovia plan to ensure that a prescription for both fluconazole and Vivjoa will be provided for patients, either electronically or via paper (if permitted). Mycovia's response refers to their response for 1f. We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 1l, regarding our concern that any applicable revisions to the Prescribing Information would need to be applied to Mycovia's proposed educational material. Mycovia states that "*All educational and promotional materials will follow the approved PI.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 4a, regarding our concern that one cannot rely on the visual aspects of the packaging to distinguish which regimen was received when being reported in the post marketing report. Mycovia states that their *"…call center vendor will utilize an intake from which details the fields that will be collected from incoming adverse drug experience (ADE) reporters. People reporting the ADEs will be questioned by the call center vendor to report the batch/lot number, the color of the package (green for fluconazole/VIVJOA or purple for VIVJOA, the NDC and additional information per the intake form. These data will be tracked in the call center vendor's electronic system and reported to Mycovia's Safety Operations team and into the Argus database."* We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 4b, regarding whether Mycovia's Pharmacovigilance/Drug Safety/AE reporting team will have access to the patient level data to ensure accurate data collection regarding the involved dosage regimen. Mycovia states "*Yes, Mycovia's Safety Operations team will have access to data collected by our call center vendor (see response to #4a) and pharmacies (Integrated Intake Pharmacy and Limited Network Pharmacy). Mycovia's call center vendor will request the following information from ADE reporters: Product name, batch number/lot number, expiration date, dose, strength, package size, NDC number, labeling color: purple for VIVJOA and green for fluconazole/VIVJOA. These data will be transferred to the Mycovia Safety Operations Argus database. Additionally, if the ADE comes from the Integrated Intake Pharmacy or Limited Pharmacy Network additional information such as date of dispense, pharmacy, prescriber name/NPI, NDC, city/state, will be collected. Mycovia can identify the dosing regimen with this information specifically the batch/lot number and the NDC.*" We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.
- We considered Mycovia's response 4c, regarding if the lot numbers for each packaging presentation would be different. Mycovia states "*Yes, the lot numbers for each packaging presentation will be different. For example, if both products were packed using the same bulk batch of capsules (CHKBB), their lot numbers would be as follows.*
    - *Vivjoa product lot number would be CHKBB1821*
    - *The fluconazole/Vivjoa product lot number would be CHKBB3721*

CHKBB is the bulk capsule lot number. For Vivjoa 18=pack count and 21=year. For fluconazole/Vivjoa 37=3 doses of fluconazole over 7 days and 21=year.
Note: The lot number first five digits and year will change but 18 and 37 will remain unchanged." We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.

- We considered Mycovia's response 4d, regarding what the acronym (b) (4) represents. Mycovia states that (b) (4) We find Mycovia's response acceptable from a medication error perspective and have no additional recommendations at this time.

In response to our recommendations, Mycovia has implemented all of our container label (blistercard) and carton labeling (child resistant wallets and outer cartons) recommendations included in the IR dated March 18, 2022 (i.e., our recommendation numbers 1d, 1i, 2a, 2b, 3a, and 5a, which align with Mycovia's responses 1d, 1h, 2a, 2b, 3a, and 5a, respectively).

However, we note that the current text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (4) the PDP) on the carton labeling (outer carton) lacks prominence . Since the proposed product will be dispensed in the individual outer carton, the differentiation and prominence of the text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" on the outer carton is important to reduce the risk of medication errors (i.e., wrong product dispensing errors). We acknowledge that when the two products (VIVJOA-only dosage regimen and fluconazole*/VIVJOA dosage regimen) are displayed side-by-side, the difference in color (purple vs. green, respectively) may provide adequate differentiation. Yet, we are concerned that the lack of prominence of the current text "fluconazole*/VIVJOA dosage regimen *fluconazole is prescribed separately" (text in (b) (4) the PDP) on the carton labeling (outer carton) may result in the descriptor being overlooked. Therefore, we recommend revising the descriptor text to be more prominent. For example:

> fluconazole*/VIVJOA dosage regimen
> *fluconazole is prescribed separately

Additionally, to provide consistency and alignment between the revised carton labeling and the currently proposed child resistant wallet, we recommend that you also box the above text on the child resistant wallet.

Furthermore, we note that included in response 2b is that Mycovia revised their fluconazole/MYCOVIA national drug code (NDC) product code from (b) (6) to "945" which we find acceptable from a medication error perspective. Thus, we find the revised fluconazole/VIVJOA container label and carton labeling, submitted March 25, 2022, acceptable from a medication error perspective and have no additional recommendations at this time.

In regard to our labeling recommendation 2c, we note that Mycovia intends to revise the prescribing information (PI) to include the fluconazole/VIVJOA NDC, as well as the information regarding the available dosage form and packaging presentation. We find this response acceptable from a medication error perspective.

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/s/

DEBORAH E MYERS
04/11/2022 04:20:18 PM

VALERIE S VAUGHAN
04/11/2022 05:17:42 PM

MISHALE P MISTRY
04/12/2022 10:03:38 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 16, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Nomenclature ana Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

On February 2, 2022, Mycovia submitted their responses[a] to our Information Request (IR) dated January 26, 2022[b], regarding the labeling submission dated January 25, 2022 for Vivjoa. Additionally, Mycovia submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons), along with their responses to our IR dated January 26, 2022. The Division of Anti-Infectives (DAI) requested that we review Mycovia's responses, as well as their revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for Vivjoa (Appendix A) to determine if they are acceptable from a medication error perspective.

[a] Response to Information Request – Labeling – Alternate Dose Regimen for Vivjoa (NDA 215888). Durham (NC): Mycovia Pharmaceuticals, Inc.; 2022 FEB 02. NDA 215888. Available at: \\CDSESUB1\evsprod\nda215888\0064\m1\us\ir-response-labeling.pdf.

[b] DiBernardo, G. FDA Communication: NDA 215888-Vivjoa (oteseconazole)-Mycovia-FDA IR on Carton and Container Labels-Sent to Applicant on 1/26/22. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 JAN 26. NDA 215888. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80640456.

2 DISCUSSION

We reviewed Mycovia's responses dated February 2, 2022, to our IR dated January 26, 2022, as well as the submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons). We note the following potential medication error concerns with Mycovia's mitigation strategies that are intended to address the concerns outlined in our February 2, 2022 IR:

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Figure 1. Mycovia's Electronic Health Record proposal to differentiate the two Vivjoa regimens

(b) (4)

We are concerned that the proposed listings might be truncated in varying computerized physician order entry (CPOE) systems and not afford the intended differentiation as intended. We acknowledge that what has been proposed is simply an example and therefore not conclusive regarding what all vendors would/may use. Thus, additional clarification is needed from Mycovia that addresses how they intend to mitigate the risk of truncated text in varying CPOE systems. Furthermore, (b) (4) we note that based on discussions with the review team, each regimen is non-inferior to the other. As such, we are concerned that the terminology (b) (4) may lead to confusion. However, using the terminology "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen provides additional clarity about how the regimens are to be administered (b) (4) (b) (4)

Additionally, based on the EHR example, the proposed fluconazole/Vivjoa dosage regimen description does not clarify that fluconazole needs to be prescribed separately (see Figure 2 below). As such, we are concerned that if a prescriber clicks on the "fluconazole/Vivjoa

regimen" dosage line to view more details of the regimen, they might incorrectly assume that fluconazole is co-packaged with Vivjoa.

Figure 2. Mycovia's proposal to describe the fluconazole/Vivjoa regimen in the Electronic Health Record

To address our concern regarding how one would ensure that one prescription for fluconazole and one prescription for Vivjoa is provided to each patient at the time of prescribing, Mycovia proposes to utilize a combination of Health Care Provider (HCP) education, customization in EHR systems, an Integrated Intake Pharmacy process (see Figure 3 below), a Limited Pharmacy Network (see Figure 3 below), and detailed dosing instructions on the package insert, carton, and container labels.

Figure 3. Mycovia's Integrated Intake Pharmacy and Limited Pharmacy Network strategic plan

With respect to the prescribing process, we note that healthcare providers will be "educated on prescribing regimens and how to prescribe each through sales force, website, and digital programs" and Mycovia "…developed a printed dosing brochure that will be provided to HCP's *[sic]*…". It is unclear how they plan to target all potential healthcare providers that will prescribe and/or dispense Vivjoa. Based on the information provided, it is also unclear whether *all* prescriptions will be prescribed via EHR and if this is the case, how this will be enforced (i.e., how to ensure that HCPs will not provide patients with paper prescriptions). Furthermore, outside of HCP education, Mycovia did not specifically articulate how they will ensure that a prescription for *both* fluconazole and Vivjoa will be provided for patients, either electronically or via paper (if permitted). On a prescription, we note that the inadvertent omission of or overlooking the descriptive text (b) (4) by the provider/pharmacist, respectively, could lead to the wrong product (i.e., Vivjoa only regimen) being dispensed. Thus, a patient may be taking fluconazole concomitantly with Vivjoa and not according to the fluconazole/Vivjoa regimen instructions. Per clinical, in this case the outcome would be unknown, as it has not been studied. However, adverse outcomes would be unlikely based on the known profiles of both products. Additionally, it is unclear whether inpatient settings of use were taken under consideration by Mycovia. Specifically, from an inpatient perspective, it is unclear how the prescription for Vivjoa would enter the Integrated Intake Pharmacy and Limited Pharmacy Network systems. Thus, additional clarification is needed.

Although Mycovia specifies that select pharmacies (i.e., Amber specialty pharmacy and Walgreens community pharmacy) will be dispensing Vivjoa, it is unclear whether other pharmacies outside of the pharmacy network would be able to order and dispense Vivjoa (for instance, if a paper prescription were brought into another pharmacy by a patient). Furthermore, it is unclear whether the prescriptions would be verified at *both* the Integrated Intake Pharmacy level and the network pharmacy level (as opposed to the Integrated Intake Pharmacy level only), to ensure that the correct product is provided to the patient.

Within Mycovia's response, we note that their proposal would rely in part on patient instruction printouts that would be provided by the pharmacy based on the compendia (i.e., Micromedex). They claim that "Drug regimens that involve multiple drugs are quite common and these print outs detail how and when to take each of the medications within the regimen." We do not agree with this statement as the printouts vary from pharmacy to pharmacy based on the resource from where the product information is captured. Furthermore, we note that the referenced "print outs" are not regulated by the Agency. Thus, instead we would recommend the FDA approved Patient Package Inserts (PPIs) (i.e., Patient Information) be provided to the patient at the time of dispensing. Additionally, we recommend that separate PPIs are developed for each Vivjoa dosage regimen, and the PPIs provide additional detail on how to take each regimen.

Mycovia also claims that the statements included on the carton labeling (b) (4) However, we disagree and note that the proposed container label and carton directions (b) (4) can be improved to better clarify that fluconazole is part of the regimen and is prescribed separately.

To address our concern related to how the two package presentations (including container labels and carton labeling) would be distinguishable in the pharmacy system, Mycovia proposes to a) use two distinct color schemes for each package as visual cues, b) include the descriptor (b) (4) on the carton labeling, and c) use non-sequential NDC product codes for each dosing regimen in conjunction with their proposed Integrated Intake Pharmacy process.

We acknowledge that to differentiate the packaging presentations, Mycovia has revised the color scheme (b) (4) to green for the fluconazole/Vivjoa regimen carton labeling, as well as added the text (b) (4) We find the revised color scheme acceptable; however, as discussed above, we are concerned (b) (4) Additionally, we find that the carton labeling can be further improved to better alert healthcare providers and patients about the need to separately administer fluconazole on days 1, 4, and 7.

We also acknowledge that Mycovia has adequately revised the NDC product code for the alternate fluconazole/Vivjoa labeling to facilitate accurate product selection. However, the prominence of the product codes for both regimens can be increased to further assist in product selection. We also note that the NDC and information regarding the available dosage form for the alternate fluconazole/Vivjoa dosage regimen is not currently included in Section 16 of the prescribing information (PI).

To address our concern regarding how one would be able to decipher which regimen/ packaging is involved in postmarketing errors, Mycovia proposes that a) differentiating features (such as the color schemes, printed dosing instructions, and non-sequential NDC codes) will enable determination of which regimen/packaging design is involved in the reported error, b) use of serialization to track and trace the product from final packaging through final shipment to patients (see Figure 4 below) c) visual features of each packaging design (e.g., color, printing of (b) (4) dosing directions) will provide additional references to readily identify which product the patient received, and d) the HCP, Integrated Intake Pharmacy and the network pharmacies will have a record of the dosage regimen.

Figure 4. Mycovia's serialization scheme

We do not agree with Mycovia that their proposal will effectively differentiate the regimens for adverse event and medication error reporting. We note that images of the products are not very often provided with postmarket reports. As such, we do not agree with Mycovia that one

can rely on the visual aspects of the packaging to distinguish which regimen was received when being reported in the post marketing report. We also note Mycovia claims that "…any product complaints or adverse events that are reported will be able to be accurately ascribed to which dosage regimen the patient receives." However, it is unclear whether Mycovia's Pharmacovigilance/Drug Safety/Adverse Event reporting team will have access to the patient level data to ensure accurate data collection regarding the involved dosage regimen. Furthermore, it is unclear whether the lot numbers for each packaging presentation would be different. Additionally, it is unclear what the acronym (b) (4) represents in Mycovia's serialization scheme (Figure 4) and as such, clarity is needed.

We note that the Division of Pharmacovigilance will be providing comments to the applicant regarding postmarket reporting.

To address our concern regarding discrepancy between the dosage instructions included in the PI versus those included on the fluconazole/Vivjoa dosage regimen packaging, the Applicant proposes to revise the container label and carton labeling to align with the PI (see Appendix A).

We acknowledge that Mycovia has addressed our concerns by revising the text for consistency with Section 2, *Dosage and Administration* in the PI. However, as discussed above, the container label and carton labeling can be further improved to clarify that fluconazole is prescribed separately for administration on days 1, 4, and 7 of the fluconazole/Vivjoa dosage regimen.

3 CONCLUSION

As currently proposed, Mycovia has not fully addressed the medication error concerns outlined in our January 26, 2022 IR. Additionally, based on the identified issues with Mycovia's proposed mitigation strategies, we provide our recommendations below in Section 4 for Mycovia to implement prior to the approval of this NDA.

Furthermore, based on Mycovia's responses dated February 2, 2022, to our IR dated January 26, 2022, as well as the submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons), we provide the following considerations for DAI:

- We recommend that the current (b) (4) terminology throughout the labeling be revised to "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen to provide addition clarity about how the regimens are to be administered (b) (4) (b) (4)
- We recommend that separate FDA approved PPIs (i.e., Patient Information) be developed and included in each product packaging, such that it is provided to the patient at the time of dispensing for each Vivjoa regimen (i.e., "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen).

4 RECOMMENDATIONS FOR MYCOVIA PHARMACEUTICALS, INC.

We refer to your responses dated February 2, 2022, to our information request (IR) dated January 26, 2022, as well as your submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for the alternative fluconazole/Vivjoa dosage regimen. As currently proposed, we have concerns with your proposed mitigation strategies, as well as the submitted revised container label and carton labeling from a medication error perspective. Thus, below we provide a list of our identified medication error issues and provide our recommendations to minimize the risk for mediation error. We recommend that our concerns be addressed, as well as our recommended revisions be implemented prior to approval of this NDA.

To provide clarity, our responses below are aligned with your February 2, 2022 responses to our IR dated January 26, 2022.

1. Regarding your response #1:
    a. As presented in your Electronic Health Record (EHR) example, we acknowledge the attempt to differentiate the regimens (i.e., (b) (4)). However, we are concerned that the listings might be truncated in varying computerized physician order entry (CPOE) systems and thus, this differentiation may not be picked up by prescribers. Thus, we are seeking additional clarification regarding your proposal to address how you intend to mitigate the risk of truncated text in various CPOE systems.
    b. Additionally, based on your EHR example, the proposed fluconazole/Vivjoa dosage regimen description does not clarify that fluconazole needs to be prescribed separately. As such, we are concerned that if a prescriber clicks on the "fluconazole/Vivjoa regimen" dosage line to view more details of the regimen, they might incorrectly assume that fluconazole is co-packaged with Vivjoa. Thus, we recommend clarifying in the EHR that fluconazole is not co-packaged with Vivjoa.
    c. It is also unclear from the information provided whether *all* prescriptions will be prescribed via EHR and if this is the case, how this will be enforced (i.e., how to ensure that HCPs will not provide patients with paper prescriptions). For example, as currently presented in Figure 1, *Description of strategic plan for Vivjoa*, we note inclusion of the text "eRx/paper fax/phone." Thus, we are seeking your clarification.
    d. The use of the terminology, (b) (4) to differentiate the regimens (b) (4) may lead to confusion. The terminology "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen provides addition clarity about how the regimens are to be administered (b) (4) (b) (4) Thus, we recommend that you revise your labeling accordingly

using the terminology “VIVJOA-only” for the Vivjoa only dosage regimen and “fluconazole/VIVJOA” for the fluconazole/Vivjoa dosage regimen.

e. We note that your response references a “Limited Pharmacy Network” which includes select pharmacies (Amber specialty pharmacy and Walgreens community pharmacy). It is unclear whether other pharmacies outside of the limited pharmacy network would be able to order and dispense Vivjoa (for instance, if a paper prescription were brought into another pharmacy by a patient).

f. Furthermore, it is unclear whether the prescriptions would be verified at both the Integrated Intake Pharmacy level and the network pharmacy level (as opposed to the Integrated Intake Pharmacy level only), to ensure that the correct product is provided to the patient.

g. We note that the inadvertent omission of or overlooking the descriptive text (b) (4) on a prescription by the provider/pharmacist, respectively, could lead to the wrong product (i.e., Vivjoa only regimen) being dispensed (along with fluconazole). Thus, a patient may be taking fluconazole concomitantly with Vivjoa and not according to the fluconazole/Vivjoa regimen instructions. Thus, we are seeking additional clarification regarding how you plan to prevent the aforementioned prescribing and subsequent dispensing error.

h. It is unclear whether you have taken into consideration the inpatient settings of use. Specifically, from an inpatient perspective, it is unclear how the prescription for Vivjoa would enter your proposed Integrated Intake Pharmacy and Limited Pharmacy Network system. Thus, we are seeking your clarification.

i. Within your proposed response, you state that the statements included on the carton labeling (b) (4) However, we disagree and note that the container label and carton directions (b) (4) (b) (4) We note that the container label and carton labeling can be improved to clarify that fluconazole (as part of the regimen) is prescribed separately, and is intended to be taken on Days 1, 4, and 7. Therefore, we recommend that you revised your current language (b) (4) to instead “On DAYS 1, 4, and 7, follow instructions for FLUCONAZOLE 150 mg (prescribed separately)” on your container label and carton labeling for the “fluconazole/VIVJOA dosage regimen.”

j. Within your proposed response, we note that your proposal would rely in part on patient instruction printouts that would be provided by the pharmacy based on the compendia (i.e., Micromedex). Additionally, you state that “Drug regimens that involve multiple drugs are quite common and these print outs detail how and when to take each of the medications within the regimen.” We do not agree with this statement as the printouts vary from pharmacy to pharmacy based on the resource from where the product information is captured. Furthermore, we note that your referenced “print outs” are not regulated by the Agency. Thus, instead we recommend the FDA approved

Patient Package Inserts (PPIs) (i.e., Patient Information) be provided to the patient at the time of dispensing. Additionally, we recommend you develop two separate PPIs for each Vivjoa dosing regimen ("VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA dosage regimen").

k. Within your response #1, it is unclear as to how you plan to target *all potential* healthcare providers that will prescribe and/or dispense Vivjoa to educate them on prescribing regimens and how to prescribe. Thus, we are seeking your clarification.

l. Outside of HCP education, you have not specifically articulated how you plan to ensure that a prescription for both fluconazole and Vivjoa will be provided for patients, either electronically or via paper (if permitted). Thus, we are seeking your clarification.

m. Additionally, please note that any applicable revisions to the Prescribing Information would need to be applied to your proposed educational material.

2. Regarding your response #2:

a. We acknowledge that to provide differentiation, you have revised the color scheme (b) (4) to green for the Vivjoa for use with fluconazole carton labeling, as well as added the text (b) (4) However, we find that the carton labeling can be further improved to inform patients about the need to separately administer fluconazole on days 1, 4, and 7.

- We recommend that you revise the text (b) (4) (b) (4) to instead "On DAYS 1, 4, and 7, follow instructions for FLUCONAZOLE 150 mg (prescribed separately)." on the carton and container labeling.
- We recommend that you revise the text under the heading "Directions" on the carton labeling (child resistant wallets and outer cartons) to instead "• On DAYS 1, 4, and 7, follow instructions for FLUCONAZOLE 150 mg (prescribed separately), then • On DAYS 14 through 20, take ONE VIVJOA 150 mg capsule once daily for 7 days (Days 14 through 20), then • Beginning on DAY 28, take ONE VIVJOA 150 mg capsule once a week (every 7 days) for 11 weeks (Weeks 4 through 14)."
- We recommend that you update the current text (b) (4) (i.e., "fluconazole/VIVJOA dosage regimen") on the carton labeling (child resistant wallets and outer cartons) to provide clarification regarding the need to take fluconazole prior to the Vivjoa capsules which are included in the alternate fluconazole/Vivjoa dosage regimen.

b. We acknowledge that you have added the national drug code (NDC) product code (b) (4) for the alternate fluconazole/Vivjoa labeling compared to the product code "823" used for the Vivjoa only labeling. Thus, we agree that you have provided product codes (middle 3-4 digits of the NDC number) that are sufficiently different between the two presentations to facilitate accurate product selection. However, to increase the prominence, we recommend that you increase the font size and bold the middle digits (product code) of the NDCs on both products.

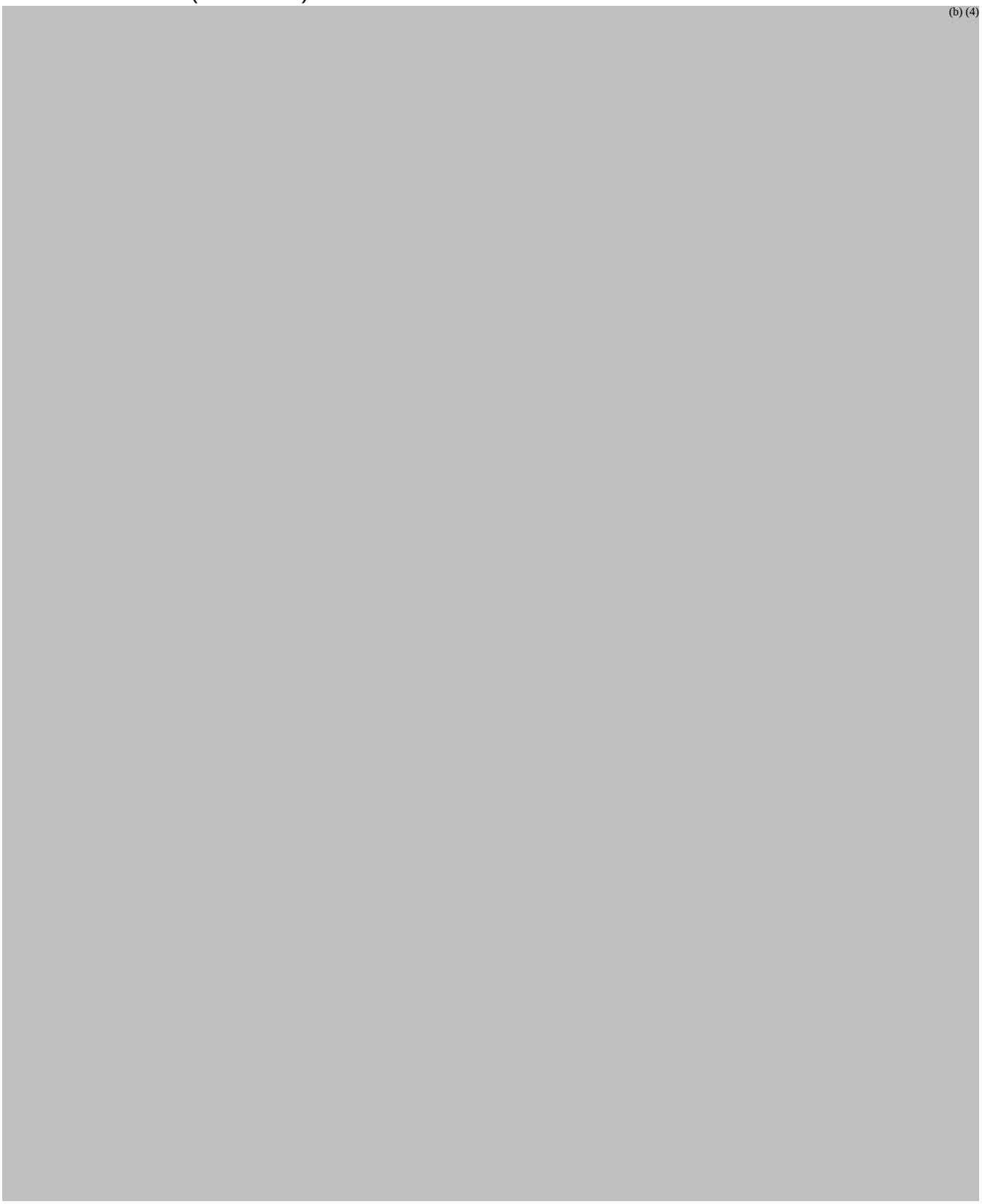
c. Additionally, we note that the NDC and information regarding the available dosage form for the Vivjoa packaging presentation intended for use with fluconazole is not currently included in the draft prescribing information (PI). Therefore, we recommend that you add the fluconazole/Vivjoa dosage regimen packaging information and corresponding NDC information to Section 16 of the PI.

3. Regarding your response #3:
   a. Refer to our recommended revisions in #2a, #2b, and #2c above.
4. Regarding your response #4:
   a. We do not agree that your proposal will be an effective differentiation for adverse event and medication error reporting. For example, you refer to "…visual features of each package design provide additional references to readily identify which product a patient received." However, we note that images are not very often provided with postmarket reports. As such, we do not agree that one can rely on the visual aspects of the packaging to distinguish which regimen was received when being reported in the post marketing report. Thus, we are seeking your clarification.
   b. We note you claim that "…any product complaints or adverse events that are reported will be able to be accurately ascribed to which dosage regimen the patient receive." However, it is unclear whether Mycovia's Pharmacovigilance/Drug Safety/AE reporting team will have access to the patient level data to ensure accurate data collection regarding the involved dosage regimen. Thus, we are seeking your clarification.
   c. It is unclear if the lot numbers for each packaging presentation would be different. Thus, we are seeking your clarification.
   d. Included in Figure 2, *Serialization scheme*, is the acronym (b) (4) It is unclear what the acronym (b) (4) represent. Thus, we are seeking your clarification.
5. Regarding your response #5:
   a. We acknowledge that you have addressed our concerns by revising the text (b) (4) to now read (b) (4) However, as previously stated, the container label and carton labeling can be further improved to clarify that fluconazole is prescribed separately for administration on days 1, 4, and 7 of the "fluconazole/VIVJOA dosage regimen" (see recommendation #2a above).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 2, 2022

Container label (Blistercard)

(b) (4)



Carton labeling (outer carton)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
03/31/2022 11:21:32 AM

VALERIE S VAUGHAN
03/31/2022 11:24:42 AM

MISHALE P MISTRY
03/31/2022 11:48:17 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 16, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Nomenclature ana Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

On February 2, 2022, Mycovia submitted their responses[a] to our Information Request (IR) dated January 26, 2022[b], regarding the labeling submission dated January 25, 2022 for Vivjoa. Additionally, Mycovia submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons), along with their responses to our IR dated January 26, 2022. The Division of Anti-Infectives (DAI) requested that we review Mycovia's responses, as well as their revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for Vivjoa (Appendix A) to determine if they are acceptable from a medication error perspective.

[a] Response to Information Request – Labeling – Alternate Dose Regimen for Vivjoa (NDA 215888). Durham (NC): Mycovia Pharmaceuticals, Inc.; 2022 FEB 02. NDA 215888. Available at: \\CDSESUB1\evsprod\nda215888\0064\m1\us\ir-response-labeling.pdf.

[b] DiBernardo, G. FDA Communication: NDA 215888-Vivjoa (oteseconazole)-Mycovia-FDA IR on Carton and Container Labels-Sent to Applicant on 1/26/22. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 JAN 26. NDA 215888. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80640456.

2 DISCUSSION

We reviewed Mycovia's responses dated February 2, 2022, to our IR dated January 26, 2022, as well as the submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons). We note the following potential medication error concerns with Mycovia's mitigation strategies that are intended to address the concerns outlined in our February 2, 2022 IR:

To address our concern pertaining to how prescribers would distinguish between the two blister packages during electronic prescribing, Mycovia proposes to: a) partner with Electronic Health Records (EHRs) integration organizations to customize EHR systems to incorporate (b) (4) **descriptors in the Computerized Physician Order Entry (CPOE) systems to distinguish the two regimens (see Figure 1 below) and b) as part of the customization, incorporate the detailed instructions for each regimen into the CPOE systems to describe how each regimen is to be taken.**

Figure 1. Mycovia's Electronic Health Record proposal to differentiate the two Vivjoa regimens

(b) (4)

We are concerned that the proposed listings might be truncated in varying computerized physician order entry (CPOE) systems and not afford the intended differentiation as intended. We acknowledge that what has been proposed is simply an example and therefore not conclusive regarding what all vendors would/may use. Thus, additional clarification is needed from Mycovia that addresses how they intend to mitigate the risk of truncated text in varying CPOE systems. Furthermore, (b) (4) we note that based on discussions with the review team, each regimen is non-inferior to the other. As such, we are concerned that the terminology (b) (4) may lead to confusion. However, using the terminology "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen provides additional clarity about how the regimens are to be administered (b) (4) (b) (4)

Additionally, based on the EHR example, the proposed fluconazole/Vivjoa dosage regimen description does not clarify that fluconazole needs to be prescribed separately (see Figure 2 below). As such, we are concerned that if a prescriber clicks on the "fluconazole/Vivjoa

regimen" dosage line to view more details of the regimen, they might incorrectly assume that fluconazole is co-packaged with Vivjoa.

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Figure 3. Mycovia's Integrated Intake Pharmacy and Limited Pharmacy Network strategic plan

With respect to the prescribing process, we note that healthcare providers will be "educated on prescribing regimens and how to prescribe each through sales force, website, and digital programs" and Mycovia "…developed a printed dosing brochure that will be provided to HCP's *[sic]*…". It is unclear how they plan to target all potential healthcare providers that will prescribe and/or dispense Vivjoa. Based on the information provided, it is also unclear whether *all* prescriptions will be prescribed via EHR and if this is the case, how this will be enforced (i.e., how to ensure that HCPs will not provide patients with paper prescriptions). Furthermore, outside of HCP education, Mycovia did not specifically articulate how they will ensure that a prescription for *both* fluconazole and Vivjoa will be provided for patients, either electronically or via paper (if permitted). On a prescription, we note that the inadvertent omission of or overlooking the descriptive text (b) (4) by the provider/pharmacist, respectively, could lead to the wrong product (i.e., Vivjoa only regimen) being dispensed. Thus, a patient may be taking fluconazole concomitantly with Vivjoa and not according to the fluconazole/Vivjoa regimen instructions. Per clinical, in this case the outcome would be unknown, as it has not been studied. However, adverse outcomes would be unlikely based on the known profiles of both products. Additionally, it is unclear whether inpatient settings of use were taken under consideration by Mycovia. Specifically, from an inpatient perspective, it is unclear how the prescription for Vivjoa would enter the Integrated Intake Pharmacy and Limited Pharmacy Network systems. Thus, additional clarification is needed.

Although Mycovia specifies that select pharmacies (i.e., Amber specialty pharmacy and Walgreens community pharmacy) will be dispensing Vivjoa, it is unclear whether other pharmacies outside of the pharmacy network would be able to order and dispense Vivjoa (for instance, if a paper prescription were brought into another pharmacy by a patient). Furthermore, it is unclear whether the prescriptions would be verified at *both* the Integrated Intake Pharmacy level and the network pharmacy level (as opposed to the Integrated Intake Pharmacy level only), to ensure that the correct product is provided to the patient.

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Mycovia also claims that the statements included on the carton labeling (b) (4) (b) (4) However, we disagree and note that the proposed container label and carton directions (b) (4) (b) (4) and can be improved to better clarify that fluconazole is part of the regimen and is prescribed separately.

To address our concern related to how the two package presentations (including container labels and carton labeling) would be distinguishable in the pharmacy system, Mycovia proposes to a) use two distinct color schemes for each package as visual cues, b) include the descriptor (b) (4) on the carton labeling, and c) use non-sequential NDC product codes for each dosing regimen in conjunction with their proposed Integrated Intake Pharmacy process.

We acknowledge that to differentiate the packaging presentations, Mycovia has revised the color scheme (b) (4) to green for the fluconazole/Vivjoa regimen carton labeling, as well as added the text (b) (4) We find the revised color scheme acceptable; however, as discussed above, we are concerned (b) (4) (b) (4) Additionally, we find that the carton labeling can be further improved to better alert healthcare providers and patients about the need to separately administer fluconazole on days 1, 4, and 7.

We also acknowledge that Mycovia has adequately revised the NDC product code for the alternate fluconazole/Vivjoa labeling to facilitate accurate product selection. However, the prominence of the product codes for both regimens can be increased to further assist in product selection. We also note that the NDC and information regarding the available dosage form for the alternate fluconazole/Vivjoa dosage regimen is not currently included in Section 16 of the prescribing information (PI).

To address our concern regarding how one would be able to decipher which regimen/ packaging is involved in postmarketing errors, Mycovia proposes that a) differentiating features (such as the color schemes, printed dosing instructions, and non-sequential NDC codes) will enable determination of which regimen/packaging design is involved in the reported error, b) use of serialization to track and trace the product from final packaging through final shipment to patients (see Figure 4 below) c) visual features of each packaging design (e.g., color, printing of (b) (4) dosing directions) will provide additional references to readily identify which product the patient received, and d) the HCP, Integrated Intake Pharmacy and the network pharmacies will have a record of the dosage regimen.

Figure 4. Mycovia's serialization scheme

We do not agree with Mycovia that their proposal will effectively differentiate the regimens for adverse event and medication error reporting. We note that images of the products are not very often provided with postmarket reports. As such, we do not agree with Mycovia that one

can rely on the visual aspects of the packaging to distinguish which regimen was received when being reported in the post marketing report. We also note Mycovia claims that "…any product complaints or adverse events that are reported will be able to be accurately ascribed to which dosage regimen the patient receives." However, it is unclear whether Mycovia's Pharmacovigilance/Drug Safety/Adverse Event reporting team will have access to the patient level data to ensure accurate data collection regarding the involved dosage regimen. Furthermore, it is unclear whether the lot numbers for each packaging presentation would be different. Additionally, it is unclear what the acronym (b) (4) represents in Mycovia's serialization scheme (Figure 4) and as such, clarity is needed.

We note that the Division of Pharmacovigilance will be providing comments to the applicant regarding postmarket reporting.

To address our concern regarding discrepancy between the dosage instructions included in the PI versus those included on the fluconazole/Vivjoa dosage regimen packaging, the Applicant proposes to revise the container label and carton labeling to align with the PI (see Appendix A).

We acknowledge that Mycovia has addressed our concerns by revising the text for consistency with Section 2, *Dosage and Administration* in the PI. However, as discussed above, the container label and carton labeling can be further improved to clarify that fluconazole is prescribed separately for administration on days 1, 4, and 7 of the fluconazole/Vivjoa dosage regimen.

3 CONCLUSION

As currently proposed, Mycovia has not fully addressed the medication error concerns outlined in our January 26, 2022 IR. Additionally, based on the identified issues with Mycovia's proposed mitigation strategies, we provide our recommendations below in Section 4 for Mycovia to implement prior to the approval of this NDA.

Furthermore, based on Mycovia's responses dated February 2, 2022, to our IR dated January 26, 2022, as well as the submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons), we provide the following considerations **for DAI**:

- We recommend that the current (b) (4) terminology throughout the labeling be revised to "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen to provide addition clarity about how the regimens are to be administered (b) (4) (b) (4)
- We recommend that separate FDA approved PPIs (i.e., Patient Information) be developed and included in each product packaging, such that it is provided to the patient at the time of dispensing for each Vivjoa regimen (i.e., "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen).

4 RECOMMENDATIONS FOR MYCOVIA PHARMACEUTICALS, INC.

We refer to your responses dated February 2, 2022, to our information request (IR) dated January 26, 2022, as well as your submitted revised container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for the alternative fluconazole/Vivjoa dosage regimen. As currently proposed, we have concerns with your proposed mitigation strategies, as well as the submitted revised container label and carton labeling from a medication error perspective. Thus, below we provide a list of our identified medication error issues and provide our recommendations to minimize the risk for mediation error. We recommend that our concerns be addressed, as well as our recommended revisions be implemented prior to approval of this NDA.

To provide clarity, our responses below are aligned with your February 2, 2022 responses to our IR dated January 26, 2022.

1. Regarding your response #1:
    a. As presented in your Electronic Health Record (EHR) example, we acknowledge the attempt to differentiate the regimens (i.e., (b) (4)). However, we are concerned that the listings might be truncated in varying computerized physician order entry (CPOE) systems and thus, this differentiation may not be picked up by prescribers. Thus, we are seeking additional clarification regarding your proposal to address how you intend to mitigate the risk of truncated text in various CPOE systems.
    b. Additionally, based on your EHR example, the proposed fluconazole/Vivjoa dosage regimen description does not clarify that fluconazole needs to be prescribed separately. As such, we are concerned that if a prescriber clicks on the "fluconazole/Vivjoa regimen" dosage line to view more details of the regimen, they might incorrectly assume that fluconazole is co-packaged with Vivjoa. Thus, we recommend clarifying in the EHR that fluconazole is not co-packaged with Vivjoa.
    c. It is also unclear from the information provided whether *all* prescriptions will be prescribed via EHR and if this is the case, how this will be enforced (i.e., how to ensure that HCPs will not provide patients with paper prescriptions). For example, as currently presented in Figure 1, *Description of strategic plan for Vivjoa*, we note inclusion of the text "eRx/paper fax/phone." Thus, we are seeking your clarification.
    d. The use of the terminology, (b) (4) to differentiate the regimens (b) (4) may lead to confusion. The terminology "VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA" for the fluconazole/Vivjoa dosage regimen provides addition clarity about how the regimens are to be administered (b) (4) (b) (4) Thus, we recommend that you revise your labeling accordingly

using the terminology “VIVJOA-only” for the Vivjoa only dosage regimen and “fluconazole/VIVJOA” for the fluconazole/Vivjoa dosage regimen.

e. We note that your response references a “Limited Pharmacy Network” which includes select pharmacies (Amber specialty pharmacy and Walgreens community pharmacy). It is unclear whether other pharmacies outside of the limited pharmacy network would be able to order and dispense Vivjoa (for instance, if a paper prescription were brought into another pharmacy by a patient).

f. Furthermore, it is unclear whether the prescriptions would be verified at both the Integrated Intake Pharmacy level and the network pharmacy level (as opposed to the Integrated Intake Pharmacy level only), to ensure that the correct product is provided to the patient.

g. We note that the inadvertent omission of or overlooking the descriptive text (b) (4) on a prescription by the provider/pharmacist, respectively, could lead to the wrong product (i.e., Vivjoa only regimen) being dispensed (along with fluconazole). Thus, a patient may be taking fluconazole concomitantly with Vivjoa and not according to the fluconazole/Vivjoa regimen instructions. Thus, we are seeking additional clarification regarding how you plan to prevent the aforementioned prescribing and subsequent dispensing error.

h. It is unclear whether you have taken into consideration the inpatient settings of use. Specifically, from an inpatient perspective, it is unclear how the prescription for Vivjoa would enter your proposed Integrated Intake Pharmacy and Limited Pharmacy Network system. Thus, we are seeking your clarification.

i. Within your proposed response, you state that the statements included on the carton labeling (b) (4) However, we disagree and note that the container label and carton directions (b) (4) (b) (4) We note that the container label and carton labeling can be improved to clarify that fluconazole (as part of the regimen) is prescribed separately, and is intended to be taken on Days 1, 4, and 7. Therefore, we recommend that you revised your current language (b) (4) to instead “On DAYS 1, 4, and 7, follow instructions for FLUCONAZOLE 150 mg (prescribed separately)” on your container label and carton labeling for the “fluconazole/VIVJOA dosage regimen.”

j. Within your proposed response, we note that your proposal would rely in part on patient instruction printouts that would be provided by the pharmacy based on the compendia (i.e., Micromedex). Additionally, you state that “Drug regimens that involve multiple drugs are quite common and these print outs detail how and when to take each of the medications within the regimen.” We do not agree with this statement as the printouts vary from pharmacy to pharmacy based on the resource from where the product information is captured. Furthermore, we note that your referenced “print outs” are not regulated by the Agency. Thus, instead we recommend the FDA approved

Patient Package Inserts (PPIs) (i.e., Patient Information) be provided to the patient at the time of dispensing. Additionally, we recommend you develop two separate PPIs for each Vivjoa dosing regimen ("VIVJOA-only" for the Vivjoa only dosage regimen and "fluconazole/VIVJOA dosage regimen").

k. Within your response #1, it is unclear as to how you plan to target *all potential* healthcare providers that will prescribe and/or dispense Vivjoa to educate them on prescribing regimens and how to prescribe. Thus, we are seeking your clarification.

l. Outside of HCP education, you have not specifically articulated how you plan to ensure that a prescription for both fluconazole and Vivjoa will be provided for patients, either electronically or via paper (if permitted). Thus, we are seeking your clarification.

m. Additionally, please note that any applicable revisions to the Prescribing Information would need to be applied to your proposed educational material.

2. Regarding your response #2:

   a. We acknowledge that to provide differentiation, you have revised the color scheme (b) (4) to green for the Vivjoa for use with fluconazole carton labeling, as well as added the text (b) (4) However, we find that the carton labeling can be further improved to inform patients about the need to separately administer fluconazole on days 1, 4, and 7.

      - We recommend that you revise the text (b) (4) (b) (4) to instead "On **DAYS 1, 4, and 7**, follow instructions for FLUCONAZOLE 150 mg (prescribed separately)." on the carton and container labeling.
      - We recommend that you revise the text under the heading "Directions" on the carton labeling (child resistant wallets and outer cartons) to instead "• On **DAYS 1, 4, and 7**, follow instructions for FLUCONAZOLE 150 mg (prescribed separately), then • On **DAYS 14 through 20**, take **ONE** VIVJOA 150 mg capsule **once daily for 7 days** (Days 14 through 20), then • Beginning on **DAY 28**, take ONE VIVJOA 150 mg capsule **once a week** (every 7 days) for 11 weeks (Weeks 4 through 14)."
      - We recommend that you update the current text (b) (4) (i.e., "fluconazole/VIVJOA dosage regimen") on the carton labeling (child resistant wallets and outer cartons) to provide clarification regarding the need to take fluconazole prior to the Vivjoa capsules which are included in the alternate fluconazole/Vivjoa dosage regimen.

   b. We acknowledge that you have added the national drug code (NDC) product code (b) (4) for the alternate fluconazole/Vivjoa labeling compared to the product code "823" used for the Vivjoa only labeling. Thus, we agree that you have provided product codes (middle 3-4 digits of the NDC number) that are sufficiently different between the two presentations to facilitate accurate product selection. However, to increase the prominence, we recommend that you increase the font size and bold the middle digits (product code) of the NDCs on both products.

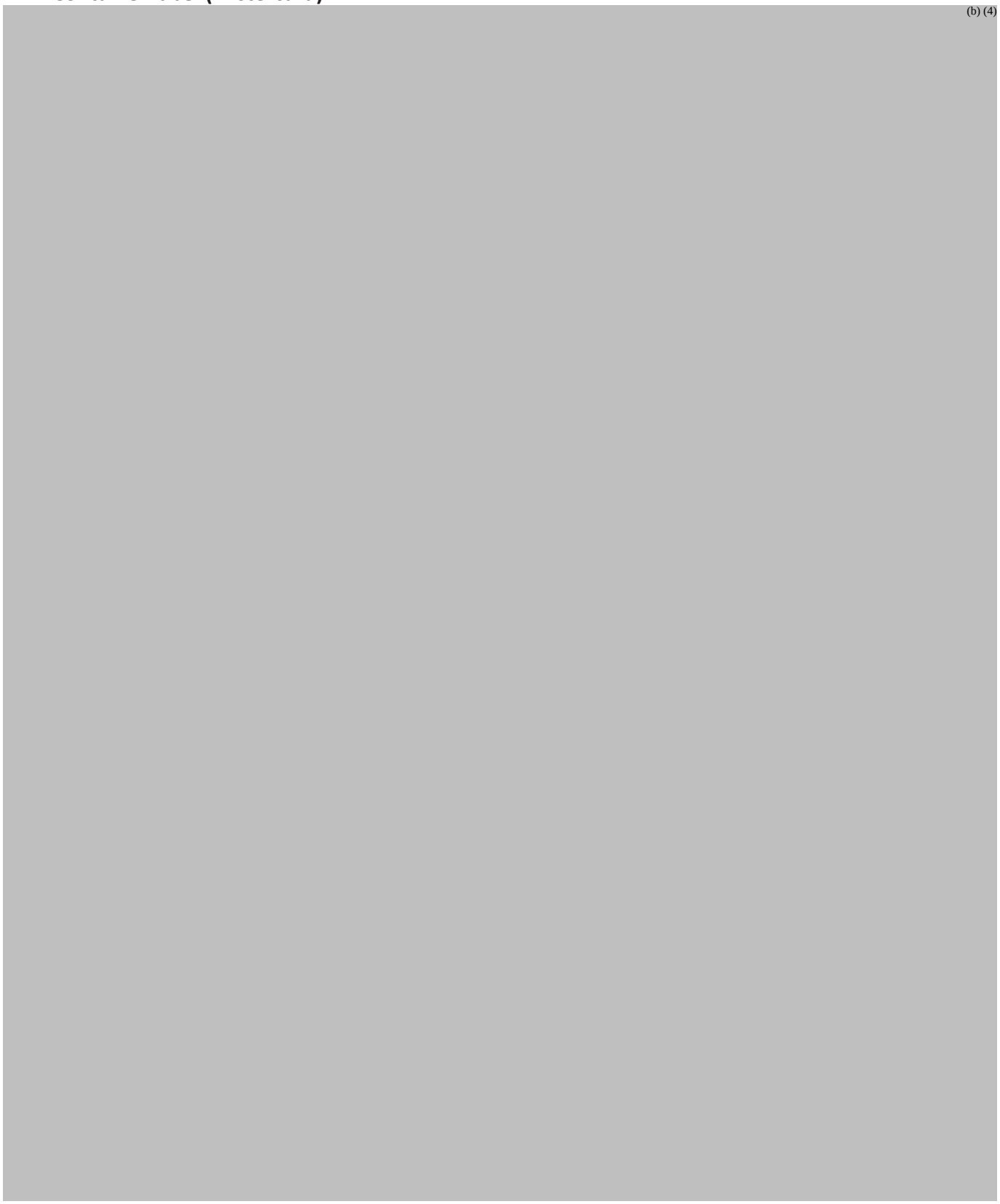
c. Additionally, we note that the NDC and information regarding the available dosage form for the Vivjoa packaging presentation intended for use with fluconazole is not currently included in the draft prescribing information (PI). Therefore, we recommend that you add the fluconazole/Vivjoa dosage regimen packaging information and corresponding NDC information to Section 16 of the PI.

3. Regarding your response #3:
   a. Refer to our recommended revisions in #2a, #2b, and #2c above.
4. Regarding your response #4:
   a. We do not agree that your proposal will be an effective differentiation for adverse event and medication error reporting. For example, you refer to "…visual features of each package design provide additional references to readily identify which product a patient received." However, we note that images are not very often provided with postmarket reports. As such, we do not agree that one can rely on the visual aspects of the packaging to distinguish which regimen was received when being reported in the post marketing report. Thus, we are seeking your clarification.
   b. We note you claim that "…any product complaints or adverse events that are reported will be able to be accurately ascribed to which dosage regimen the patient receive." However, it is unclear whether Mycovia's Pharmacovigilance/Drug Safety/AE reporting team will have access to the patient level data to ensure accurate data collection regarding the involved dosage regimen. Thus, we are seeking your clarification.
   c. It is unclear if the lot numbers for each packaging presentation would be different. Thus, we are seeking your clarification.
   d. Included in Figure 2, *Serialization scheme*, is the acronym (b) (4) It is unclear what the acronym (b) (4) represent. Thus, we are seeking your clarification.
5. Regarding your response #5:
   a. We acknowledge that you have addressed our concerns by revising the text (b) (4) However, as previously stated, the container label and carton labeling can be further improved to clarify that fluconazole is prescribed separately for administration on days 1, 4, and 7 of the "fluconazole/VIVJOA dosage regimen" (see recommendation #2a above).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 2, 2022

Container label (Blistercard)

(b) (4)



Carton labeling (outer carton)

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DEBORAH E MYERS
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VALERIE S VAUGHAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 28, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Prescribing Information (PI) and an additional container label (blistercard) and carton labeling (child resistant wallets and outer cartons) for Vivjoa, received on January 25, 2022. The Division of Anti-Infectives (DAI) requested that we review the revised PI, additional container label (blistercards), and carton labeling (child resistant wallets and outer cartons) for Vivjoa (Appendix A) to determine if they are acceptable from a medication error perspective.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

As part of our assessment, we reviewed the revised Prescribing Information (PI) received on January 25, 2022. We note that the revised PI includes two dosage regimens, that is:

- a VIVJOA-only dosage regimen:
  - (b) (4)
- an Alternate fluconazole/VIVJOA dosage regimen:
  - (b) (4)
    - (b) (4).

- [redacted] (b) (4)
- **Beginning on Day 28:** Administer VIVJOA 150 mg orally once a week (every 7 days) for 11 weeks (Weeks 3 through (b) (4)).

As proposed, the Dosage and Administration section of the PI does not include guidance for practitioners to help facilitate selection between the two dosage regimens, which could lead to confusion. Our DAI colleagues confirmed that practitioners can select either regimen to use for the proposed indication and also indicated that there is no difference in efficacy between the two regimens. Our DAI colleagues further clarified that the alternative fluconazole/VIVJOA regimen is included based on collective safety and efficacy data received for three clinical studies, of which one study used an oteseconazole-only regimen while two of the three studies used a fluconazole/oteseconazole regimen. In light of the additional fluconazole/VIVJOA dosage regimen, the Applicant has proposed an additional 18-count blister package configuration to be used for the fluconazole/VIVJOA dosage regimen.

We previously reviewed the proposed 18-count blister package intended for use with the VIVJOA-only regimen.[a] Our evaluation of the two proposed 18-count blister package configurations identified areas of concerns that increase the risk of medication error that exists within the medication use process. For example, it is unclear whether the following has been considered:

- As it relates to prescribing, it is unclear how prescribers would distinguish between the two blister packages during electronic prescribing. Additionally, it is unclear how the two regimens and subsequent selection of packaging would be distinguished if a prescription is written with the instructions "Use as directed" or "UAD." Moreover, it is unclear how one would ensure that one prescription for fluconazole and one prescription for Vivjoa is provided to the patient at the time of prescribing.
- As it relates to transcribing into the pharmacy system, it is unclear how the two 18-count blister package presentations would be distinguishable from one another. We are concerned that there may be product selection errors at this stage in the medication use process.
- As currently presented, the container labels, carton labeling, and packaging between the two blister presentations are identical (i.e., same color scheme, etc.), which increases the risk of selection errors from the pharmacy shelf. Moreover, it is unclear if the National Drug Code (NDC), specifically the product code (middle 3-4 digits of the NDC number), will be sufficiently different between the two blister presentations to facilitate accurate product selection. Postmarketing experience indicates that similarity (e.g., sequential numbering) of the product code has led to selection and dispensing errors.
- Lastly, as it relates to postmarketing monitoring, it is unclear how one would be able to decipher which regimen/packaging is involved in potentials errors that are reported.

[a] Myers, D. Label and Labeling Review Memo for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 22. RCM No.: 2021-1075-1.

Furthermore, we identified additional concerns with the new proposed blister package configuration intended to be used for the fluconazole/VIVJOA regimen. As currently proposed:

- Text on the proposed container label for the alternative fluconazole/Vivjoa dosage regimen (i.e., (b) (4)) is inconsistent with the proposed alternate fluconazole/VIVJOA dosage regimen in the PI (i.e., (b) (4) Beginning on Day 28: Administer VIVJOA 150 mg orally once a week (every 7 days) for 11 weeks (weeks 3 through 14).
- Similarly, text on the back panels of the Child resistant wallet and Carton labeling (outer carton) (i.e., (b) (4)) as directed.) is inconsistent with the proposed alternate fluconazole/VIVJOA dosage regimen in the PI.

Thus, as currently designed, we are concerned that patients may not understand that they need to take only fluconazole in week 1 and that patients may administer Vivjoa and fluconazole concomitantly starting on Day 1, resulting in medication errors.

3 CONCLUSION

Given the above considerations, the proposed blister packaging submitted for the alternative fluconazole/Vivjoa dosage regimen is not designed to support safe and effective use. Thus, we recommend the Applicant re-design the new proposed blister package to address the concerns outlined above.

The above assessment was shared with our DAI colleagues and our concerns were communicated to the Applicant on January 26, 2022.[b]

[b] DiBernardo, G. FDA Communication: NDA 215888-Vivjoa (oteseconazole)-Mycovia-FDA IR on Carton and Container Labels-Sent to Applicant on 1/26/22. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 JAN 26. NDA 215888. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80640456.

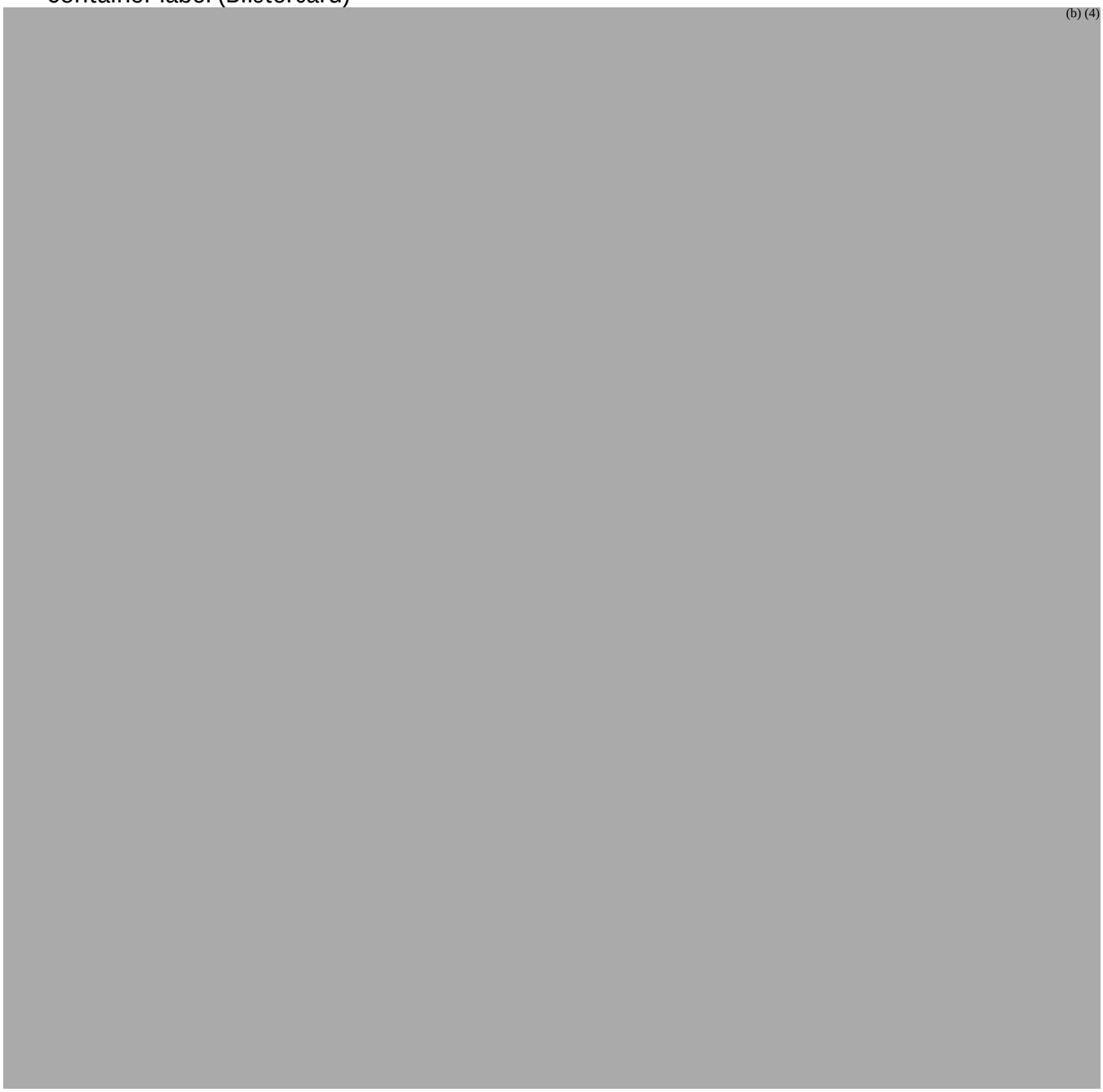
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 25, 2022

Prescribing Information (Image not shown)

- Prescribing Information, received on January 25, 2022 and available at: \\CDSESUB1\evsprod\nda215888\0062\m1\us\draft-labeling-text-tracked.docx.

Container label (Blistercard)

(b) (4)



Carton labeling (outer carton)

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/s/

DEBORAH E MYERS
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VALERIE S VAUGHAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 22, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc. (Mycovia)
OSE RCM #:	2021-1075-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) received on January 20, 2022 for Vivjoa. The Division of Anti-Infectives (DAI) requested that we review the revised container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) for Vivjoa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION AND RECOMENDATAIONS FOR DAI

The Applicant implemented all of our recommendations for their submitted 18-count container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) for the proposed indication of recurrent vulvovaginal candidiasis. However, as the labeling negotiations surrounding the indication, as well as dosage and recommendation continue, we note that the 18-count container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) for the Agency's proposed alternate fluconazole/Vivjoa dosing regimen for the proposed indication of recurrent vulvovaginal candidiasis, as well as the

[a] Myers, D. Label and Labeling Review for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-1075.

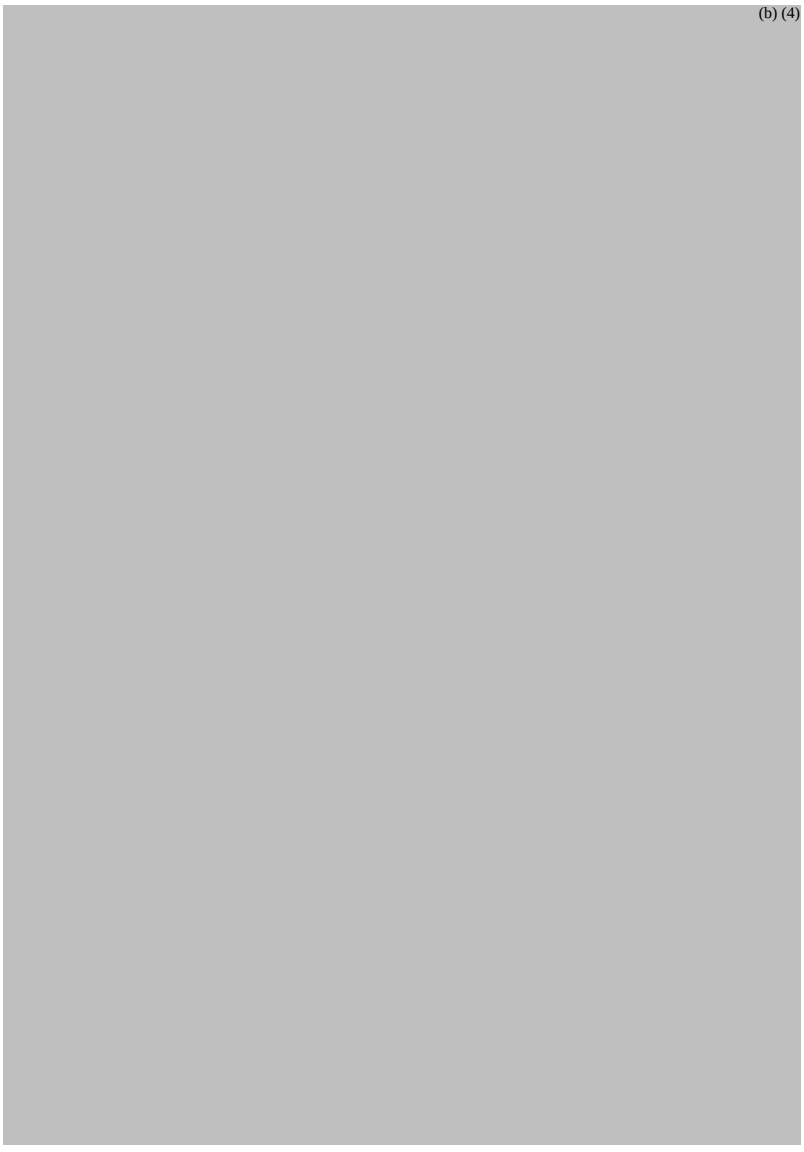
(b) (4) were not submitted for our review. Therefore, based on the outcome of ongoing labeling negations; if the Applicant agrees to with the Agency's proposed alternate fluconazole/Vivjoa dosing regimen for the proposed indication of recurrent vulvovaginal candidiasis, we request that the Applicant submit their proposed 18-count container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) for our review. (b) (4) We recommend that the Applicant consider our recommendations made during our previous label and labeling review for any additional applicable container label(s) and carton labeling.[b]

[b] Myers, D. Label and Labeling Review for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-1075.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 20, 2022

Container label (Blistercard)

Child resistant wallet



Carton labeling (outer carton)

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VALERIE S VAUGHAN
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 10, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215888
Product Name and Strength:	Vivjoa (oteseconazole) Capsules, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mycovia Pharmaceuticals, Inc (Mycovia)
FDA Received Date:	May 27, 2021, August 5, 2021, and November 9, 2021
OSE RCM #:	2021-1075
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vivjoa (oteseconazole) Capsules, the Division of Anti-Infectives (DAI) requested that we review the proposed Vivjoa prescribing information (PI), patient package insert (PPI), container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Response to Information Request	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION

During our review of the labels and labeling for Vivjoa we noted that the proposed 18-count blister packaging is labeled with two frequencies of dosage (i.e., days and weeks) to supply a total of 12 weeks of oteseconazole therapy. As presented, patients are to take a loading dose of 7 capsules over 2 days (i.e., 4 capsules on day 1, then 3 capsules on day 2), followed by once weekly dosing starting on week 2 (day 14) for 11 weeks. The proposal to include two frequencies on this blister packaging is unique in comparison to other blister packaged products currently on the market, which use only one unit of frequency, daily or weekly (e.g., Medrol Dosepak, Actonel, etc.).

We are concerned that the inclusion of two frequencies could lead to confusion and result in dosing error, for example, inadvertent administration of all 18 capsules over a 12 to 18-day period if the labeled “week” is overlooked or assumed to be “day” given the regimen starts with daily dosing. To gain a better understanding of the clinical consequence to dosing error (i.e., administering all 18 capsules over a 12 to 18-day period), we inquired about the clinical consequences via information request to the Applicant. In response, the Applicant indicated that oteseconazole was safely administered at daily doses of 600 mg for 14 days in 184 subjects

as well as daily doses of 300 mg for 7 days in 84 subjects and 14 days in 106 subjects, which resulted in total doses up to 8,400 mg compared to 2,700 mg for the currently proposed labeled dosing for oteseconazole. The Applicant further stated that if all 18 capsules were to be taken over 13 days there will unlikely be clinical consequence as oteseconazole safety was observed at higher dose in multiple studies (see Appendix E for additional details). We conferred with our DAI clinical colleagues who indicated that the *clinical safety profile of the drug appears quite benign, outside of the unexplained CPK elevations for which the Sponsor reported that there are no dose effect from a PK standpoint*[a].

Based on the above, we find that inadvertent administration of all 18 capsules over a 12 to 18-day period is not likely to lead to significant adverse effects; however, we find that the 18-count blister packaging could be further optimized to better differentiate daily dosing from weekly dosing. Thus, we provide a recommendation in Section 6 below for the Applicant.

Additionally, based on dosage revisions proposed by DAI, to update the PI, Section 2 *Dosing and Administration* to include an alternative fluconazole/oteseconazole dosage regimen, the labeling of the current proposed blister packaging does not support this alternative dosage regimen, (b) (4) As such, additional consideration is needed regarding a packaging presentation that would support the proposed alternative dosage regimen.

However, we note that the addition of a second blister package, to support the alternative dosage regimen (fluconazole/oteseconazole), could result in two 18-count blister packages containing identical active ingredients (oteseconazole), dosage form (capsules), strength (150 mg), and quantity of capsules (18). As such, this could pose challenges for how the national drug code (NDC) numbers would be listed, since both packages would contain the same active ingredients, dosage form, strength, and quantity of capsules. Additionally, we are concerned that even if the NDCs are different for the different 18-count packages, the difference in NDC numbers may not provide adequate differentiation to prevent potential medication errors. Thus, we are concerned about potential dosing errors and dispensing errors if the wrong 18-count blister package is dispensed. We acknowledge that Mycovia's intent of proposing labeled directions on their blister packaging was in an effort to enhance adherence (i.e., facilitate the correct dosing by the patient) to the prescribed dosing. Therefore, we are concerned that completely eliminating the labeled direction on the blistered packaging may weaken this mitigation strategy.

Thus, as Mycovia develops their new proposed container label and carton labeling for the aforementioned alternative fluconazole/oteseconazole dosing regimen, as well as their

[a] Re: NDA 215888 SN0055 – Information Request – Clinical/Clinical Pharmacology – CPK. Durham (NC): Mycovia Pharmaceuticals, Inc; 2021 DEC 07. Available at: \\CDSESUB1\evsprod\nda215888\0055\m1\us\resp-fda-ir.pdf.

updated proposed container label and carton labeling for their 18-count package, we recommend that they consider the concerns outlined above.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient package insert (PPI), container labels (blistercards), carton labeling (child resistant wallets), and carton labeling (outer cartons) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Mycovia Pharmaceuticals, Inc.

5 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented in the Prescribing Information (PI), there is a lack of clarity (b) (4) As presented, the PI appears to lack recommended dosage instructions for the proposed (b) (4) indication.	Lack of clarity in how the medication is to be taken (b) (4) could lead to prescribing and administration errors.	Clarify the intended recommended dosage (b) (4) Additionally, in conjunction with the identified issued, we note that revisions to the packaging presentation may be needed to ensure that the recommended dosage can be achieved (b) (4) We ask that DAI takes this into consideration as they clarify the intended recommended dosage for each labeled indication.
2.	The proposed proprietary name,	The proposed proprietary name, Vivjoa, was found	Add the proprietary name, Vivjoa, as appropriate

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	"Vivjoa," is missing in the Prescribing Information.	conditionally acceptable on September 14, 2021.[b]	throughout the proposed prescribing information and patient package insert (PPI).
3.	As currently presented in the Highlights of Prescribing Information, under the header "Dosage and Administration" and in the FPI – subsection 2.1 *Dosing Information,* we note the use of the abbreviation "VVC" which is not defined.	Abbreviations can be a source of misinterpreted and result in confusion if not appropriately defined.	Eliminate or define the abbreviation "VVC" with its intended meaning "vulvovaginal candidiasis." For example, chang (b) (4) "Recurrent VVC" to read "Recurrent vulvovaginal candidiasis." Or, if preferred, ensure the first appearance of the abbreviation "VVC," is defined. For example, revise to "vulvovaginal candidiasis (VVC)…" following the initial mention of the term 'vulvovaginal candidiasis' under the Highlights of Prescribing Information and following the initial mention of the term 'vulvovaginal candidiasis' in the FPI.
Highlights of Prescribing Information			
1.	As currently presented, under the header "Dosage and Administration" we note that the proposed dosage statement, (b) (4)	Lack of clarification could result in inappropriate schedule of product administration or wrong dose medication errors.	To help avoid inappropriate schedule of product administration or wrong dose medication errors, clarify the appropriate intended dose schedule (b) (4)

[b] Myers, D. Proprietary Name Review for Vivjoa (NDA 215888). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2021 SEP 14. PNR ID No.: 2021-1044724082.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) does not provide clarification (b) (4)		(b) (4)
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, under subsection 2.1, *Dosing Information*, we note that the proposed (b) (4) does not provide clarification (b) (4)	Lack of clarification (b) (4) could result in inappropriate schedule of product administration medication errors.	To help avoid inappropriate schedule of product administration medication errors, include the appropriate intended dose schedule (b) (4)
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the National Drug Code (NDC) number is not included.	To facilitate identification of the dosage form, the NDC number is required per 21 CFR 201.57(c)(17)(iii).	The Applicant has provided their intended NDC numbers (i.e., (b) (4) 74695-823-18 for the 18-count) on their proposed carton labeling (child resistant wallets and outer boxes). In accordance with 21 CFR 201.57(c)(17)(iii), the proposed NDC numbers will need to be added to the *How Supplied* section once finalized.
2.	Based on dosage revisions proposed by DAI to update the PI, that is, to remove (b) (4) is no longer supported.		We recommend removal of the current text (b) (4) as it is not supported by the revisions proposed by DAI to update the PI, Section 2 *Dosing and Administration*.
Patient Package Insert			
1.	The Patient Package Insert (PPI) does not include instructions regarding missed doses.	Patients may attempt to take multiple tablets at once (e.g., during the weekly maintenance phase) to account for a previously missed dose.	We recommend "missed dose" instructions be included in the PPI to clarify to patients the appropriate steps to take if they inadvertently miss a dose. We defer to the Division of Medical Policy Programs (DMPP) Patient Labeling Team (PLT) for additional recommendations for the PPI.

6 RECOMMENDATIONS FOR MYCOVIA PHARMACEUTICALS, INC

Table 3. Identified Issues and Recommendations for Mycovia Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (blistercards) and Carton Labeling (child resistant wallets and outer cartons)			
1.	As currently presented, the strength statement on the container label (blistercards) and carton labeling (child resistant wallets and outer cartons) is "150 mg" without specifying that the strength is per capsule.	Wrong dose medication errors could occur if users misinterpret the strength statement (i.e., 150 mg) on the container label (blistercard of (b) (4) 18 capsules) and carton labeling as the total strength of the package contents (i.e., 150 mg ((b) (4) (b) (4) 18 x 150 mg capsules)), instead of the strength of a single capsule.	To address the risk of misinterpretation of the strength statement and to provide consistency throughout the package labeling (i.e., container label (blistercards) and carton labeling (child resistant wallets and outer cartons)), we recommend revising all occurrences of the strength statement "150 mg" to "150 mg per capsule" using consistent size and color of the font.
2.	As currently presented, the proposed container labels (blistercards) includes, (b) (4) and the proposed carton labeling (child resistant wallets and outer cartons) includes, (b) (4) However, the directions included do not provide clarification regarding if the 4 capsules and 3 capsules dosages are	Lack of clarification regarding if the 4 capsules and 3 capsules dosages, for Days 1 and 2 respectively, are intended to be taken as a single dose or instead spread throughout the days (i.e., one capsule four times daily and one capsule three times daily respectively) could result in inappropriate schedule of product administration medication errors.	To help avoid inappropriate schedule of product administration medication errors, include the appropriate intended dose schedule for the 4 capsules and 3 capsules dosages (i.e., as a single dose or instead spread throughout the days) on the container labels (blistercards) and carton labeling (child resistant wallets and outer cartons).

Table 3. Identified Issues and Recommendations for Mycovia Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	intended to be taken as a single dose or instead spread throughout the days (i.e., one capsule four time daily and one capsule three times daily respectively).		
Container Labels (blistercards)			
1.	As currently presented, the linear barcode is missing on the (b) (4) (b) (4) 18-count container labels (blistercards).	The drug linear barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label and is required per 21 CFR 201.25(c)(2).	Ensure that a linear barcode is included on the (b) (4) 18-count container labels (blistercards) in accordance with 21 CFR 201.25(c)(2) if the blistercards are intended to be separated from the blister wallet. If the blistercards are physically attached to the blister wallet you may instead, or in addition to the inclusion on the container labels (blistercards), include the linear barcode the blister wallet. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
Carton Labeling (child resistant wallets and outer cartons)			
1.	As currently presented, the net quantity statements (i.e., (b) (4) (b) (4) 18-count	The product strength statement is considered to be "critical information." For more information see	We recommend that you increase the prominence of the strength statement (i.e., "150 mg"), for example, by

Table 3. Identified Issues and Recommendations for Mycovia Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	capsules) is bolded and more prominent than your strength statement (150 mg).	the draft guidance for industry, "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*".[c]	increasing the font size (height), bolding, and/or adding color to the strength statement. In addition, we recommend decreasing the prominence of the net quantity statements (i.e., (b) (4) (b) (4) 18-count capsules).
Packaging			
1.	As currently presented, the 18-count blister packaging includes two frequencies of dosage (i.e., days and weeks) which could inadvertently lead to medication error.	Dosing error could occur if patients inadvertently overlook the change from daily to weekly dosing for the 12 week treatment course (e.g., administering all 18 capsules over a once daily schedule instead of as intended).	Incorporate additional mitigation to facilitate differentiation of the daily versus weekly schedules. For example, consider revising "day" and "week" to appear in contrasting colors to help bring additional attention to the change from daily dosing on days 1 and 2 to weekly dosing starting on day 14.

[c] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vivjoa that Mycovia Pharmaceuticals, Inc submitted on November 9, 2021.

Table 4. Relevant Product Information for Vivjoa	
Initial Approval Date	N/A
Active Ingredient	oteseconazole
Indication	(b) (4)
Route of Administration	Oral
Dosage Form	Capsules
Strength	150 mg
Dose and Frequency	(b) (4) (b) (4)
How Supplied	In (b) (4) 18-count blister package within a child resistant wallet. There will be one blister pack per wallet and one wallet per outer carton.
Storage	Oteseconazole should be stored at 20°C to 25°F (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) and protected from light when removed from the outer carton. [*See USP Controlled Room Temperature*]
Container Closure	Blister packs are comprised of a clear film and aluminum lidding, that will be put into a child-resistant cardboard wallet which is placed within an outer cardboard carton. The (b) (4) clear film is composed of (b) (4) film suitable for pharmaceutical packaging. The push through lidding is composed of aluminum foil (b) (4) typically used in pharmaceutical packaging. The child-resistant cardboard wallet meets the Federal standards for safety required by the Poison Prevention Packaging Act of 1970, a standard promulgated by the Consumer Product Safety Commission as one which reasonably protects children from

	entering packaging that would contain potentially harmful substances. (16 CFR Part 1700.20, July 21, 1995). The blister packaging will be housed within a child-resistant cardboard wallet. The cardboard wallet does not come into contact with the capsules. The cardboard wallet is placed within an outer carton to provide protection from light.

APPENDIX E. RESPONSE TO INFORMATION REQUEST

Applicant's Response to Agency's December 2, 2021 Information Request, received on December 10, 2021 and available at: \\CDSESUB1\evsprod\nda215888\0057\m1\us\fda-ir-resp.pdf.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Vivjoa labels and labeling submitted by Mycovia Pharmaceuticals, Inc

- Container labels (blistercards) received on November 9, 2021
- Carton labeling (child resistant wallet) received on November 9, 2021
- Carton labeling (outer carton) received on November 9, 2021
- Prescribing Information (PI) received on November 9, 2021
    - Draft (clean labeling) available at the following link: \\CDSESUB1\evsprod\nda215888\0047\m1\us\draft-labeling-text-clean.docx.
    - Annotated (track changes labeling) available at the following link: \\CDSESUB1\evsprod\nda215888\0047\m1\us\draft-labeling-text-tracked-v2.docx.
- Patient Package Insert (PPI) received on August 5, 2021
    - Draft (clean labeling) available at the following link: \\CDSESUB1\evsprod\nda215888\0014\m1\us\draft-patient-label.docx.

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	December 27, 2021
To:	Gregory F. DiBernardo Chief, Project Management Staff **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** James Dvorsky, PharmD **Team Lead** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VIVJOA (oteseconazole)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 215888
Applicant:	Mycovia Pharmaceuticals, Inc.

1 INTRODUCTION

On May 25, 2021 Mycovia Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 215888 for VIVJOA (oteseconazole) capsules, for oral use. VIVJOA is an azole antifungal with the proposed indication for the reduction of recurrent vulvovaginal candidiasis (RVVC) in females who are not of reproductive potential.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on September 2, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VIVJOA (oteseconazole) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft VIVJOA (oteseconazole) capsules, for oral use PPI received on May 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on December 21, 2021.
- VIVJOA (oteseconazole) capsules, for oral use PPI received on May 25, 2021, revised by the Review Division throughout the review cycle, and received by OPDP on December 21, 2021.
- Draft VIVJOA (oteseconazole) capsules, for oral use Prescribing Information (PI) received on May 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on December 21, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/23/21

To: Caroline Jjingo, M.D., MPH, Clinical Reviewer
Division of Anti-Infective Products (DAI)

Gregory DiBernardo, Regulatory Project Manager, (DAI)

From: James Dvorsky, Team Lead
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Vivjoa (oteseconazole)

NDA: 215888

In response to DAI's consult request dated 9/2/21, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA/BLA submission for Vivjoa.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DAI on 12/21/21 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on 11/9/21, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact James Dvorsky at (301) 796-2655 or james.dvorsky@fda.hhs.gov.

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Clinical Inspection Summary

Date	13 December 2021
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Gregory DiBernardo, RPM Caroline Jjingo, MD, Medical Reviewer Thomas Smith, MD, Medical Team Leader Division of Anti-Infectives (DAI)
NDA #	215888
Applicant	Mycovia Pharmaceuticals, Inc.
Drug	Oteseconazole
NME	Yes
Proposed Indication	(b) (4)
Consultation Request Date	12 July 2021
Summary Goal Date	17 December 2021
Action Goal Date	27 January 2022
PDUFA Date	27 January 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this application (NDA 215888), routine PDUFA inspections were conducted for 7 clinical investigators: Drs. Gorgacz, Miller, Kasparian, Iglesias, Moraru, Maximos, and Mosher. The inspections covered three clinical studies: VMT-VT-1161-CL-011 (CL-011), VMT-VT-1161-CL-012 (CL-012), and VMT-VT-1161-CL-017 (CL-017).

During the inspections, the primary efficacy endpoint source data [i.e., the investigator's assessments of vulvovaginal (VVC) signs and symptoms and mycology culture test results through Week 48 for Protocols CL-011 and CL-012 and through Week 50 for Protocol CL-017] were verified against the sponsor's data line listings for all subjects randomized at these 7 sites. Several discrepancies in the investigator's total composite VVC signs and symptoms score were noted at 5 of the 7 sites (i.e., Drs. Gorgacz, Miller, Kasparian, Iglesias, and Moraru). In addition, certified copies of the mycology culture results from the central laboratories were verified against the sponsor's data line listings for all subjects randomized at these 7 sites. One discrepancy in the mycology culture test results was noted at Dr. Gorgacz's site. These discrepancies (in the investigator's total composite VVC signs and symptoms scores and the mycology culture test results) would have no impact on the overall

efficacy results of the three protocols. These discrepancies are described in more detail in Section III of this Clinical Inspection Summary (CIS).

Two data reliability concerns related to the following were identified during the inspections:

- Accidental unblinding events: Unblinding events were noted to have occurred as a result of an Interactive Web Response System (IWRS) programming error, impacting 6 subjects enrolled in Protocols CL-011 and CL-012 at two of the 7 sites inspected (i.e., Drs. Miller and Kasparian). In a 13 Sep 2021 response to an Information Request, the applicant noted that the IWRS Service Provider programmed the IWRS incorrectly so that the system would send an automated email disclosing the subject's treatment assignment to the site user who performed a subject's randomization. The applicant stated that this IWRS programming error resulted in the unblinding of the subjects' treatment assignment for 24 subjects at 16 different sites who were enrolled between 3 Oct to 27 Nov 2018.

  The IWRS service provider reportedly corrected the IWRS programming error on 28 Nov 2018. The unblinded site staff at the 16 different sites continued to perform their delegated study-related duties, which ranged from obtaining medical/medication histories to administering subject questionnaires, assessing AEs, and performing physical exams, including pelvic exams. Because it is difficult to definitively know if the unblinded site staff shared the contents of the email with other study staff, we recommend that a sensitivity analysis be conducted with regard to the efficacy data generated from the 24 subjects noted in the applicant's 13 Sep 2021 response in order to determine the robustness of the reported overall efficacy results.

- Subject ineligibility: At Dr. Iglesias' site, there were 4 subjects (i.e., Subjects 31246(b) (6), 31246(b) (6) 31246(b) (6) and 31246-(b) (6)) who did not meet core inclusion criteria to support a history of recurrent VVC and/or diagnosis of acute VVC. The details of the ineligibility of these 4 subjects are discussed in more detail in Section III of the CIS. These ineligible subjects were not identified during the sponsor's routine monitoring visits and were not reported to FDA in the listing of protocol deviations in the Clinical Study Report (i.e., Appendix 16.2.2.2) or the BIMO data line listing of protocol deviations (i.e., listing 7.1). Of note, according to the Clinical Study Report, all of these subjects were excluded from the modified intent-to-treat (mITT) population and the per-protocol population except for Subject 31246(b) (6). This subject was included in the per-protocol population but should have been excluded.

Notwithstanding the ineligible subjects, unblinding events, and recommendations noted above, the data otherwise generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 215888 was submitted in support of the use of oral oteseconazole (b) (4) The key studies supporting the application were the following:

- VMT-VT-1161-CL-011 (CL-011), "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis"
- VMT-VT-1161-CL-012 (CL-012), "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis"
- VMT-VT-1161-CL-017 (CL-017), "A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules versus Fluconazole and Placebo in the Treatment of Acute Vulvovaginal Candidiasis Episodes in Subjects with Recurrent Vulvovaginal Candidiasis"

Protocol CL-011:

- ***Subjects:*** A total of 553 subjects were screened; 438 were enrolled in the Induction Phase of the study and 326 were randomized in the maintenance phase of the study: 217 subjects received oteseconazole and 109 subjects received placebo; 182 subjects receiving oteseconazole and 91 subjects receiving placebo completed the study.
- ***Sites:*** 97 sites in the United States (U.S.), Bulgaria, Canada, Japan, Poland, and the United Kingdom (U.K.)
- ***Study initiation and completion dates:*** (b) (6) (first patient enrolled) to (b) (6) (b) (6) (last patient completed)
- ***Initial Database Lock Date:*** 30 Nov 2020; ***Final Database Lock Date:*** 2 Dec 2020
- ***Study Unblinding:*** 3 Dec 2020

Protocol CL-012:

- ***Subjects:*** A total of 534 subjects were screened; 425 were enrolled in the Induction Phase of the study and 330 were randomized in the maintenance phase of the study: 220 subjects received oteseconazole and 110 subjects received placebo; 191 subjects receiving oteseconazole and 91 subjects receiving placebo completed the study.
- ***Sites:*** 84 sites in the U.S., Belgium, Czech Republic, Hungary, Romania, and Ukraine.
- ***Study initiation and completion dates***: (b) (6) (first patient enrolled) to (b) (6) (last patient completed)
- ***Initial Database Lock Date:*** 30 Nov 2020; ***Final Database Lock Date:*** 1 Dec 2020
- ***Study Unblinding:*** 3 Dec 2020

Protocol CL-017:

- ***Subjects:*** A total of 251 subjects were screened; 219 were randomized in the Induction Phase (147 were randomized to the oteseconazole group and 72 were randomized to the fluconazole/placebo group), and 185 subjects entered the maintenance phase (123 in the oteseconazole group and 62 in the fluconazole/placebo group). A total of 112 subjects in

the oteseconazole group and 55 subjects in the fluconazole/placebo group completed the study.
- **Sites:** 51 sites in the U.S.
- ***Study initiation and completion dates:*** (b) (6) (first patient enrolled) to (b) (6) (last patient completed)
- ***Final Database Lock Date:*** 22 Dec 2020
- ***Study Unblinding:*** 22 Dec 2020

Protocols CL-011 and CL-012 were identical in design, and Protocol CL-017 was similar in design. All three protocols were phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies.
- Protocols CL-011 and CL-012 were designed to evaluate the efficacy and safety of oral oteseconazole capsules in the treatment of patients aged 12 and older with recurrent VVC through Week 48.
- Protocol CL-017 was designed to evaluate the efficacy and safety of oral oteseconazole capsules versus fluconazole and placebo in the treatment of acute VVC episodes in subjects with recurrent VVC and also to evaluate the efficacy of oral oteseconazole in the prevention of culture-verified acute episodes of VVC through Week 50 in recurrent VVC subjects.

For all 3 studies, there was an Induction Phase and a Maintenance Phase.

For Protocols CL-011 and CL-012:

During the Induction Phase, all subjects presenting with acute VVC infections received open label fluconazole 150 mg orally every 72 hours for 3 doses. Subjects returned approximately 14 days after the first dose of fluconazole for evaluation and if the acute VVC infection had resolved (defined by a signs and symptoms score of <3), they entered the Maintenance Phase.

During the Maintenance Phase, subjects were randomized in a 2:1 ratio via an IWRS to receive one of the following:
- Oteseconazole 150 mg once daily X 7 days, followed by oteseconazole 150 mg once weekly for 11 weeks
- Matching placebo for 12 weeks

If the acute VVC infection had not resolved (defined by a signs and symptoms score of ≥3), the subject was considered a screen failure and encouraged to see their physician for further evaluation and follow-up care. The duration of individual subject participation was approximately 50 weeks, including the 2-week Induction Phase with fluconazole administration, followed by 12 weeks of IP administration, and 36 weeks of follow up.

The ***primary efficacy outcome measure*** was the proportion of subjects with 1 or more culture-verified acute VVC episodes during the Maintenance Phase in the Intent-to-Treat (ITT) Population. The Maintenance Phase was defined as post randomization through Week 48 of the study. An acute VVC episode during the Maintenance Phase (considered a recurrent

episode) was defined as a positive culture for Candida species and a total composite signs and symptoms score of ≥3 (as assessed by the investigator).

The investigator's assessments of VVC signs and symptoms and vaginal swab for fungal cultures were obtained at Screening, Baseline, Day 14, Week 6, and then every 6 weeks thereafter until end-of-study (EOS), Week 48.

For Protocol CL-017:

During the Induction Phase, subjects were randomized via an IWRS in a 2:1 ratio to one of the following:

- Oteseconazole 600 mg (4x150 mg capsules) on Day 1 and oteseconazole 450 mg (3x150 mg capsules) on Day 2 together with matching fluconazole placebo capsules every 72 hours for 3 doses
- Fluconazole 150 mg every 72 hours for 3 doses together with matching oteseconazole placebo capsules on Day 1 and Day 2

During the Maintenance Phase, subjects returned approximately 14 days after the first dose of oteseconazole or fluconazole for evaluation and, if the acute VVC infection had resolved (defined by a signs and symptoms score of <3), they entered the Maintenance Phase to receive one of the following:

- Subject initially randomized to receive oteseconazole received oteseconazole 150 mg once weekly for 11 weeks
- Subject initially randomized to receive fluconazole received a matching placebo regimen for 11 weeks

Subjects then entered into a 37-week follow-up period after they received oteseconazole or placebo weekly for 11 weekly doses.

The ***primary efficacy outcome measure*** was the proportion of subjects with one or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT population, which included the subjects who failed clearing their infection during the Induction Phase. An acute VVC episode (considered a recurrent episode) is defined as a positive culture for Candida species and a clinical signs and symptoms score of ≥3.

The investigator's assessment of clinical signs and symptoms and vaginal swab for fungal cultures were obtained at Screening (Day 1), Day 14, Week 8, and then every 6 weeks thereafter until end-of-study (EOS), Week 50.

Use of Central Laboratories:

Vaginal swabs were sent to a central laboratory for testing as follows:

- Protocols CL-011, CL-012, CL-017: North American sites shipped vaginal swabs for testing (b) (4) (b) (4)

- Protocols CL-011 and CL-012: European sites shipped vaginal swabs for testing [redacted]
- Protocol CL-011: Japanese sites shipped vaginal swabs [redacted] On receipt at [redacted] the samples were then shipped [redacted] for testing

Certified copies of the source records for the mycology culture test results from the central laboratories were provided to clinical investigator sites at the end of the study for record retention and inspection purposes.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history.

III. RESULTS (by site):

1. **Marek Gogacz, MD**
   Site # 27156
   ul. Przerwy - Tetmajera 21
   Lublin, 20-362
   Poland
   PDUFA Inspection Dates: 4 to 8 Oct 2021

At this site for Protocol CL-011, 43 subjects were screened, 30 were randomized, and 21 subjects completed the study. Nine subjects were terminated early from the study. Seven of the nine subjects terminated early for unspecified reasons—4 of the 7 subjects were randomized to oteseconazole (i.e., Subjects 27156[redacted] 27156[redacted] 27156[redacted] and 27156-[redacted]), and 3 of the 7 were randomized to placebo (i.e., Subjects 27156[redacted] 27156[redacted] and 27156[redacted]). One subject (Subject 27156[redacted], randomized to placebo) terminated early due to a pregnancy and 1 subject (Subject 27156[redacted] randomized to placebo) missed the final two study visits due to COVID-19 pandemic-related issues but did not formally withdraw consent.

A full audit of the study records for the 30 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 48); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting

culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 48) were reviewed and verified against the sponsor's data line listings for the 30 randomized subjects. The following discrepancies were noted when comparing the source records against the sponsor's data line listings.

Subject Number/ Randomization	**Visit/Date**	**Source records**	**Sponsor's BIMO data line listings**
27156 (b) (6) oteseconzaole	Week 42 (b) (6)	Investigator total composite VVC signs and symptoms score: 2	Investigator total composite VVC signs and symptoms score: 0
27156 (b) (6) oteseconzaole	Week 36 (b) (6)	Mycology culture test report: sample cancelled	Mycology test report: no yeast isolated

Reviewer's comments: *The minor discrepancy in the composite VVC signs and symptoms score for Subject 27156 (b) (6) does not affect the overall primary efficacy outcome as an acute VVC episode was defined as a positive culture for Candida species and an investigator total composite VVC signs and symptoms score of ≥3. In addition, the cancelled mycology culture test for Subject 27156 (b) (6) at the Week 36 Visit has no impact on the overall primary efficacy outcome because this subject did not meet the protocol definition of a VVC episode, as her total composite VVC signs and symptoms score was 0 at that same visit. These discrepancies were discussed with Dr. Gogacz during the inspection closeout meeting. Dr. Gogacz acknowledged the discrepancies and promised improvements in the future.*

2. Jane Miller, MD
Site #31136
1241 South White Street
New Orleans, LA 70125
PDUFA Inspection Dates: 2 to 5 August 2021

At this site for Protocol CL-011, 28 subjects were screened, 16 were randomized, and 11 subjects completed the study. Subjects 31136 (b) (6) and 31136 (b) (6) withdrew due to moving out of the area; Subject 31136 (b) (6) withdrew due to an amputation secondary to a motor vehicle accident; Subject 31136 (b) (6) terminated early due to a pregnancy; and Subject 31136 (b) (6) was lost to follow-up (all 5 subjects who did not complete the study were randomized to oteseconazole).

A full audit of the study records for the 28 screened subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 48); adverse event reporting;

protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 48) were reviewed and verified against the sponsor's data line listings for the 16 randomized subjects. The following discrepancies were noted when comparing the source records against the sponsor's data line listings.

Subject Number/ Randomization	**Visit/Date**	**Source Records: Investigator total composite VVC signs and symptoms score**	**Sponsor's BIMO data line listings: Investigator total composite VVC signs and symptoms score**
31136-(b) (6) oteseconzaole	Unscheduled (b) (6)	12	0
31136(b) (6) oteseconzaole	Week 24 (b) (6)	1	0

Reviewer's comment: *These discrepancies are unlikely to affect the primary efficacy outcome as a VVC episode was defined as a positive culture for Candida species and an investigator total composite VVC signs and symptoms score of ≥3. Although Subject 31136-(b) (6) had a total composite VVC signs and symptoms score of 12 noted in the source records from the unscheduled visit (b) (6) the mycology culture result for that same date was "no yeast isolated," and therefore, as reported in the sponsor's data line listings, this subject did not meet the protocol definition of a VVC episode. These discrepancies were discussed with Dr. Miller during the inspection closeout meeting. Dr. Miller acknowledged the transcription errors and promised improvements in their quality control check process for critical data.*

Accidental unblinding of the following 4 subjects was also observed during inspection.

- Subject 31136(b) (6) (randomized to oteseconazole)
- Subject 31136(b) (6) (randomized to oteseconazole)
- Subject 31136(b) (6) (randomized to oteseconazole)
- Subject 31136(b) (6) (randomized to placebo)

This accidental unblinding occurred as a result of an IWRS programming error. The IWRS service provider responsible for programming the IWRS incorrectly programmed it to send an IWRS-automated email disclosing the subject's treatment assignment to the site user who performed a subject's randomization.

Reviewer's comment: *The unblinding issue was further discussed with Dr. Miller during the inspection. Dr. Miller explained that only the main study coordinator received the IWRS-automated emails that contained the unblinding information, and this study coordinator did not open, read, or share the emails and unblinding information with other site staff. Because it is difficult to definitively know if the study coordinator (who is no longer employed at this site) read, distributed, or shared the contents of the emails with other staff, a sensitivity*

analysis should be conducted with regard to efficacy data generated from these 4 subjects at this site to determine the robustness of the reported overall efficacy study results.

3. Masayasu Nomura, MD
Site #26160
Chuo-ku Namba 4-4-4-6F
Osaka-shi, Osaka-Fu 542-0076
Japan
PDUFA Inspection Dates: Inspection cancelled due to travel-restrictions related to COVID-19 pandemic

A consult to conduct an inspection at this site (Site 26160) was received from DAI on 12 July 2021. At that time, the COVID-19 global pandemic had significantly limited our ability to conduct international on-site GCP inspections, including in Japan. In addition, ORA was unable to conduct a remote regulatory review of the site due to Japan's patient privacy restrictions and language barriers. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for an inspection of this site in support of NDA 215888 was reevaluated. Following discussions between OSI and DAI, a decision was made that assessment of the application could proceed without a GCP inspection of this site. OSI was therefore unable to determine if Protocol CL-011 was conducted adequately and whether the study data at this site were reliable in support of the proposed indication.

4. Stephen Kasparian, MD
Site #31147
1151 Robeson Street, Suite 202
Fall River, MA 02720
PDUFA Inspection Dates: 30 August to 2 September 2021

At this site for Protocol CL-011, 16 subjects were screened, 13 were randomized, and 12 subjects completed the study. Subject 31147 (b) (6) (randomized to oteseconazole) withdrew consent due to moving out of the area.

A full audit of the study records for the 16 screened subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 48); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 48) were reviewed and verified against the

sponsor's data line listings for the 13 randomized subjects. The following discrepancies were noted when comparing the source records against the sponsor's data line listings.

Subject Number/ Randomization	**Visit/Date**	**Source Records: Investigator total composite VVC signs and symptoms score**	**Sponsor's data line listings: Investigator total composite VVC signs and symptoms score**
31147 (b) (6) oteseconzaole	Unscheduled (b) (6)	2	Missing
31147 (b) (6) placebo	Unscheduled (b) (6)	4	Missing
31147 (b) (6) placebo	Unscheduled (b) (6)	2	Missing
31147 (b) (6) oteseconzaole	Unscheduled (b) (6)	4	2
31147 (b) (6) oteseconzaole	Week 6 (b) (6)	0	1
31147 (b) (6) oteseconzaole	Unscheduled (b) (6)	1	Missing

Reviewer's comment: *These minor discrepancies in the total composite VVC signs and symptoms scores do not affect the primary efficacy outcome as an acute VVC episode was defined as a positive culture for Candida species and an investigator total composite VVC signs and symptoms score of ≥3. Of note, Subjects 31147 (b) (6) and 31147 (b) (6) had an investigator total composite VVC signs and symptoms score of 4 noted on the source records during their unscheduled visits (b) (6) respectively. However, the mycology culture test results source records from those dates were "no yeast isolated," and therefore, as reported in the sponsor's data line listings for those unscheduled visits, these subjects did not meet the protocol definition of an acute VVC episode.*

A Form FDA 483 was issued at the end of the inspection that included the finding of inadequate and inaccurate records. Dr. Kasparian adequately responded to the inspection findings in a letter dated 15 Sep 2021. He acknowledged the transcription errors and missing entries in the EDC system and promised improvements in their quality control check process.

Accidental unblinding of the following 2 subjects was also observed during inspection.

- Subject 31147 (b) (6) (randomized to oteseconazole)
- Subject 31147 (b) (6) (randomized to oteseconazole)

This accidental unblinding occurred as a result of an IWRS programming error. The IWRS service provider responsible for programming the IWRS incorrectly programmed it to send an IWRS-automated email disclosing the subject's treatment assignment to the site user who performed a subject's randomization.

Reviewer's comment: *The unblinding issue was further discussed with the site staff during the*

inspection. The site staff explained that only one study coordinator received the IWRS-automated emails that contained the unblinding information for the two subjects and that this study coordinator opened and read the emails. Moreover, this study coordinator continued to perform her study-related duties. Also, because it is difficult to know if the study coordinator shared the contents of the emails with other staff, a sensitivity analysis should be conducted with regard to efficacy data generated from these 2 subjects at this site to determine the robustness of the reported overall efficacy study results.

5. Nayvis Iglesias, MD
Site #31246
3971 SW 8th St, Suite 209
Miami, FL 33134
PDUFA Inspection Dates: 22 to 29 July 2021

At this site for Protocol CL-012, 23 subjects were screened, 13 were randomized, and 10 subjects completed the study. Three subjects terminated early; Subject 31246(b) (6) (randomized to oteseconazole) terminated early per sponsor request and Subjects 31246(b) (6) (randomized to oteseconazole) and 31246(b) (6) (randomized to placebo) withdrew consent.

A full audit of the study records for the 13 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VCC signs and symptoms and all mycology culture test results through Week 48); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

An adverse event of increased vaginal bleeding in Subject 31246(b) (6) (randomized to oteseconazole) was not reported to the sponsor. This adverse event was noted in the source records (i.e., study adverse event log) to have occurred on (b) (6) and to have resolved on (b) (6) It was classified as Grade 1 (mild) and was deemed by the investigator to be unrelated to the study drug.

Reviewer's comment: *The missing adverse event data of increased vaginal bleeding in Subject 31246(b) (6) is unlikely to impact the overall safety results of the study because it is an isolated event. In addition, it was not classified as serious and was deemed by the investigator to be unrelated to the study drug.*

The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 48) were reviewed and verified against the sponsor's data line listings for the 13 randomized subjects. The following discrepancies were noted when comparing the source records against the sponsor's data line listings.

Subject Number/ Randomization	Visit/Date	Source Records: Investigator total composite VVC signs and symptoms score	Sponsor's data line listings: Investigator total composite VVC signs and symptoms score	Does the discrepancy affect the subject's eligibility?
31246 (b) (6) oteseconazole	Screening (b) (6)	11	10	No
31246 (b) (6) placebo	Screening (b) (6)	9	8	No
31246 (b) (6) placebo	Baseline (b) (6)	3	2	Yes

Reviewer's comment: *The discrepancies for Subjects 31246 (b) (6) and 31246 (b) (6), which occurred at their Screening Visits, do not affect their eligibility because their composite VVC scores were ≥ 3. Inclusion criteria #3 states the following:*

"Subjects must have an acute VVC episode at Screening, defined as:

a) a total signs and symptoms score of ≥3 and
b) a positive KOH wet mount preparation or Gram stain from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells."

The discrepancy for Subject 31246 (b) (6) affects her study eligibility because she did not meet inclusion criteria #4, which states, "Subjects must have a composite VVC signs and symptoms score of less than 3 at the Baseline (Day 1) Visit." This subject had a total composite VVC signs and symptoms score of 3 at the Baseline (Day 1) Visit (i.e., the original recording found on the paper source records). This discrepancy was not found or corrected during the sponsor's routine monitoring visits and was not reported to FDA in the listing of protocol deviations (i.e., Appendix 16.2.2.2) in the BIMO listing of protocol deviations (i.e., listing 7.1).

Subject 31246 (b) (6) who did not meet inclusion criteria #4 as described above, also did not have documentation to support a prior episode of VVC documented with a positive laboratory diagnosis as stated in inclusion criteria #2 of the protocol. Inclusion criteria #2 states, "Subjects must have a history of recurrent VVC as defined by three (3) or more patient reported and/or laboratory confirmed episodes of acute VVC in the past 12 months including the episode confirmed at Screening, with at least one episode (not including the current episode) documented by a positive culture, PCR, Affirm test, KOH test, Gram stain, or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells, or other approved diagnostic tests."

Three additional subjects were also noted to not meet study eligibility criteria as follows:

- Subjects 31246 (b) (6) (randomized to placebo) and 31246 (b) (6) (randomized to oteseconazole) did not meet inclusion criteria #2. These subjects had no source records to support a prior episode of VVC documented with a positive laboratory diagnosis.

- Subject 31246 (b) (6) (randomized to oteseconazole) had a composite VVC signs and symptoms score of 4 at the Baseline (Day 1) Visit and thus did not meet inclusion criteria #4 which states that subjects must have a composite VVC signs and symptoms score of less than 3 at the Baseline (Day 1) Visit. Moreover, the investigator also did not confirm that this subject did not meet exclusion criteria #1, which states, "Subjects must not have the presence of concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, Trichomonas vaginalis, Chlamydia trachomatis, or Neisseria gonorrhoeae) at Screening visit and at the Day 1 visit if an infection is suspected." For this subject, there were no laboratory results available from the testing that was performed to confirm that the current infection was not secondary to Chlamydia and Neisseria gonorrhoeae. The endocervical swab samples were obtained at screening on (b) (6) and obtained again at an unscheduled visit on (b) (6) Both test samples were incorrectly collected and were subsequently cancelled. The subject was randomized on (b) (6)

Reviewer's comment: *These 4 subjects (i.e., Subjects 31246 (b) (6) 31246 (b) (6) 31246 (b) (6) and 31246 (b) (6)) did not meet core inclusion criteria to support a history of recurrent VVC and/or diagnosis of acute VCC. The ineligibility of these 4 subjects who did not meet core inclusion criteria was not found during the sponsor's routine monitoring visits and was not reported to FDA in the listing of protocol deviations (i.e., listing 16.2.2.2) in the Clinical Study Report or the BIMO listing of protocol deviations (i.e., listing 7.1). Of note, according to Clinical Study Report, these subjects were excluded (for other reasons) from the mITT population in addition to the per-protocol population, except for Subject 31246 (b) (6). This subject was included in the per-protocol population but should have been excluded.*

Also noted during inspection was that 10 of the 13 randomized subjects had no screening HbA1c testing performed. Six of the 10 subjects were randomized to oteseconazole (i.e., Subjects 31246 (b) (6) 31246 (b) (6) 31246 (b) (6) 31246 (b) (6) 31246 (b) (6) and 31246 (b) (6)) and 4 of the 10 subjects were randomized to placebo (i.e., Subjects 31246 (b) (6) 31246 (b) (6), 31246 (b) (6) and 31246 (b) (6)). Section 9.1.5.3 of the protocol (version 2 and beyond) states that testing for HbA1c should be performed for all subjects at Screening. Moreover, exclusion criteria #14 states that subjects must not have poorly controlled diabetes mellitus (HbA1c ≥8.5% at Screening; performed by the investigator site).

Reviewer's comment: *The missing HbA1c testing was discussed with Dr. Iglesias during the inspection closeout meeting. She explained that blood and urine glucose levels were monitored throughout the study, including at Screening, for these subjects. She further stated that elevated blood and urine glucose levels would have been indicators of a potential diabetic subject, and automatic laboratory alerts would have notified her accordingly. Although not conducting the study according to the protocol is a regulatory violation, these missed HbA1c laboratory tests are unlikely to have an impact on the overall efficacy and safety results of the study as none of these 10 subjects experienced elevated blood and urine glucose levels that might be indicative of uncontrolled diabetes mellitus.*

A Form FDA 483 was issued to Dr. Iglesias at the inspection close-out meeting that included the previously described inspection observations for failure to maintain adequate and accurate case histories (i.e., related to the missing adverse event, transcription errors and

data discrepancies) and for failure to conduct the investigation in accordance with the signed statement of the investigator and investigational plan (i.e., related to the subject ineligibility issue and missing HbA1c testing). Dr. Iglesias responded to the inspection findings in a letter dated 18 Aug 2021, acknowledging them and stating that she plans to implement improvements in their training processes for verifying subject eligibility and in their quality control check process.

6. Rodica Moraru, MD
Site #28213
No. 3-5 Dr. Sergiu Dumitru Street
Bucaresti, 011025
Romania
PDUFA Inspection Dates: 13 to 17 Sep 2021

At this site for Protocol CL-012, per the sponsor's data line listings, 43 subjects were screened, 15 were randomized, and 9 subjects completed the study. Six subjects were terminated early for unspecified reasons. Four of the 6 were randomized to oteseconazole (i.e., Subjects 28213-(b) (6) 28213-(b) (6), 28213(b) (6) and 28213(b) (6)) and 2 of the 6 were randomized to placebo (i.e., Subjects 28213(b) (6)0 and 28213(b) (6)).

A full audit of the study records for the 15 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 48), adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 48) were reviewed and verified against the sponsor's data line listings for the 15 randomized subjects. The following discrepancies were noted when comparing the source records against the sponsor's data line listings.

Subject Number/ Randomization	**Visit/Date**	**Paper source CRFs: total composite VVC signs and symptoms score**	**Sponsor's data line listings: total composite VVC signs and symptoms score**
28213(b) (6) oteseconazole	Week 12 (b) (6)	1	0
28213(b) (6) placebo	Baseline (b) (6)	1	0

Reviewer's comments: *These minor discrepancies in the composite VVC signs and symptoms scores do not affect the primary efficacy outcome as an acute VVC episode was defined as a positive culture for Candida species and an investigator total composite VVC signs and symptoms score of ≥3. In addition, the minor discrepancy for Subject 28213 (b) (6) at the Baseline Visit did not affect her eligibility to participate in the study because she still met inclusion criteria #4, which states, "Subjects must have a composite VVC signs and symptoms score of less than 3 at the Baseline (Day 1) Visit."*

7. Bassem Maximos, MD
Site # 58
651 N Egret Bay Blvd, Suite H
League City, TX 77573
PDUFA Inspection Dates: 7 to 10 Sep 2021

At this site for Protocol CL-017, 20 subjects were screened, all of whom were randomized, and 17 subjects completed the study. Per the sponsor's BIMO data line listings, 3 subjects were terminated early from the study due to induction failure: Subject 58 (b) (6) (randomized to oteseconazole) on Study Day 22, Subject 58 (b) (6) (randomized to oteseconazole) on Study Day 16, and Subject 58 (b) (6) (randomized to fluconazole/ placebo) on Study Day 27.

A full audit of the study records for the 20 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 50), adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 50) were reviewed and verified against the sponsor's data line listings for the 20 randomized subjects. No discrepancies were noted.

8. Leanna Mosher, MD
Site # 26
4320 Wornall Rd #720
Kansas City, MO 64111
PDUFA Inspection Dates: 23 to 26 August 2021

At this site for Protocol CL-017, 14 subjects were screened, 13 were randomized, and 11 subjects completed the study. Per the sponsor's BIMO data line listings, Subject 26 (b) (6) (randomized to fluconazole/placebo) was discontinued on Study Day 14 due to induction failure and Subject 26 (b) (6) (randomized to oteseconazole) was lost to follow-up.

A full audit of the study records for the 13 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data related to culture-verified acute VVC episodes (i.e., the investigator's assessments of VVC signs and symptoms and all mycology culture test results through Week 50), adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records documenting culture-verified acute VVC (i.e., the investigator's assessments of VVC signs and symptoms and mycology culture test results through Week 50) were reviewed and verified against the sponsor's data line listings for the 13 randomized subjects. No discrepancies were noted.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
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cc:
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DAI/Project Manager/Gregory Di Bernardo
DAI/Clinical Reviewer/Caroline Jjingo
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OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/s/

CHERYL A GRANDINETTI
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-215888
Submission Number	030
Submission Date	9/23/2021
Date Consult Received	9/24/2021
Drug Name	Oteseconazole (Vivjoa capsule)
Indication	(b) (4) recurrent vulvovaginal candidiasis
Therapeutic Dose	600 mg dose on Day 1 followed by 450 mg on Day 2 and then 150 mg once weekly doses from Day 14 for 11 weeks
Clinical Division	DAI
Protocol Review	Link (extracted from SP)

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 9/24/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-111675 dated 12/09/2019 in DARRTS (link);
- Sponsor's clinical study protocol # VMT-VT-1161-CL-018 (SN0030, link);
- Sponsor's statistical analysis plan # VMT-VT-1161-CL-018 (SN0030, link);
- Sponsor's clinical study report # VMT-VT-1161-CL-018 (SN0030, link);
- Investigator's brochure Ver. 8.0 under IND-111675 (SN0093; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0030; link).

1 SUMMARY

In the thorough QT study, no significant QTcF prolongation effect of oteseconazole was detected.

The effect of oteseconazole (VT-1161) was evaluated in a thorough QT study (Study # VMT-VT-1161-CL-018). This was a double-blind, randomized, multiple-dose, placebo- and positive-controlled, crossover study evaluating the effect of oteseconazole on the QT/QTc interval in healthy female subjects. Assay sensitivity was established by the moxifloxacin. The highest dose evaluated was 1200 mg (600 mg on Days 1 to 13 and 1200 mg on Day 14) which offers ~5-fold margin over the maximum therapeutic exposures (Cmax: ~2679.3 ng/mL) associated with the proposed dosing regimen and is expected to cover the worst-case exposure scenario (renal impairment, Section 3.1). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest

that VT-1161 is associated with increases in the QTcF interval (refer to Section4.5) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Concentration** (ng/mL)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Oteseconazole (VT-1161)	12597.1	-5.6	(-10.5 to -0.8)

Administered as 600 mg on Days 1 to 13 and 1200 mg on Day 14For further details on the FDA analysis, please see section 4.

Findings of this analysis are further supported by the available by-time analysis (Section 4.3) and categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

None.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to SDN001 (link). Below is the proposed text from the CSS-IRT for 'Cardiac Electrophysiology' Section of the label (*addition*). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics *Cardiac Electrophysiology* *At 5 times the maximum exposures for the approved recommended dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Mycovia Pharmaceuticals, Inc. is developing oteseconazole for (b) (4) (b) (4) vulvovaginal candidiasis (b) (4) Oteseconazole (VT-1161; MW: 527.39 g/mol) is an antifungal agent.

The product is formulated as an immediate-release hard gelatin capsule formulation containing 150 mg oteseconazole (anhydrous) for oral administration. The maximum proposed therapeutic dose includes 600 mg dose on Day 1 followed by 450 mg on Day 2 and then 150 mg once weekly doses from Day 14 for 11 weeks. The maximum peak concentrations of ~2679.3 ng/mL (Tmax: 4 to 6 h; half-life: ~ 4126h) are expected during maintenance phase with the proposed dosing regimen (Week 14, pseudo steady state; Study # CL-017). Considering long the half-life (95% CI: 3776 - 4476 hours), significant accumulation is expected with multiple dosing at the proposed dosing regimen. The maximum studied dose is 600 mg daily for 14 days followed by once weekly for 22 weeks (Cmax: 11570 ng/mL; Study # CL-007).

The human mass balance study indicates that ~56% of the drug (as TR) is excreted in feces, and ~26% (as TR) is excreted in urine (Study # CL-016). Sponsor claims that oteseconazole is not significantly metabolized (<1% of parent) by the CYP450 enzymes (minor CYP1A2) and highlights that it has a low drug interaction potential as a victim drug. The sponsor states that no major changes are expected in the exposure of oteseconazole in subjects with renal impairment or hepatic impairment based on its slow clearance and the long half-life.

To characterize the risk of QT prolongation of oteseconazole, the sponsor conducted a thorough QT study to (Study VMT-VT-1161-CL-018). This was a double-blind, randomized, multiple dose (600 mg on Days 1 to 13 and 1200 mg on Day 14), placebo- and positive-controlled, crossover study evaluating the effect of oteseconazole on the QT/QTc interval in healthy female subjects using concentration QT as primary analysis. For protocol review, refer to the previous IRT review under IND-111675 dated 12/10/2019 in DARRTS. The peak concentration (Cmax: 12597 ng/mL) on Day 14 observed with the studied dosing regimen (i.e., 600 mg on Days 1 to 13 and 1200 mg on Day 14) is expected to offer ~4.7-fold margin over the maximum therapeutic exposures (Cmax: ~2679.3 ng/mL) associated with the proposed dosing regimen (during the maintenance phase).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety and previous IRT review under IND-111675 dated 12/10/2019 in DARRTS.

The expected peak concentrations of 2679.3 ng/mL (Free: 51 nM; PPB: >99%) during maintenance phase with the proposed dosing (i.e., 600 mg dose on Day 1 followed by 450 mg on Day 2 and then 150 mg once weekly doses from Day 14 for 11 weeks) offers higher than ~37-fold margin (hERG IC50: 1.9 µM).

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for VT-1161 was based on exposure-response analysis, please see Section 3.2.3 for additional details.

ECG parameters and change from baseline were summarized by cohort and time point with number of subjects, mean, SD, minimum, median, and maximum. Baseline was defined as the last pre-dose measurement on Day 1.

Reviewer's comment: *The sponsor used descriptive statistics for QTcF and change from baseline at each timepoint. FDA reviewer used statistical model to analyze the ECG data. Thus, the sponsor's results are not directly comparable with reviewer's assessment. The overall profile is similar to reviewer's analysis results.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms.

Reviewer's comment: The results of the sponsor's analysis shows that the study demonstrated assay sensitivity. Please see Section 4.5.1 for additional details.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no subjects with QTcF >500 msec in any of the cohorts per the sponsor's analysis, but there was 1 subject with QTcF >60 msec change from baseline for cohort 2B control (Placebo/Moxifloxacin) group. There were few subjects with HR >100 beats/min per the sponsor's analysis. There were no significant outliers per the sponsor's analysis for PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to sponsor's analysis results. Sponsor reported one subject who had QTcF >60 msec change from baseline, which was observed after receiving Moxifloxacin. Therefor that subject is not included in reviewer's outlier table. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between plasma concentration of VT-1161 and ΔΔQTcF (placebo corrected change from baseline in QTcF) using a linear mixed-effects approach on all subjects in the analysis data set for cardiac assessment. The sponsor analysis indicates a slight negative slope of −0.00022 ms per ng/mL (90% CI: −0.000379 to 0.000059) in concentration-QTc relationship. The model predicted ΔΔQTcF (upper confidence interval) values of -4.40 (-1.86) msec at the mean peak concentrations for the highest dose studied (1200 mg: geomean Cmax ~12550 ng/mL) following oral administration on Day 14. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic doses (i.e., 600 mg

dose on Day 1 followed by 450 mg on Day 2 and then 150 mg once weekly doses from Day 14 for 11 weeks with maximum Cmax of ~2679.3 ng/mL during the maintenance phase).

Reviewer's comment: *Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Cardiac Safety Analysis

There were no deaths or serious AEs. Two subjects were discontinued from the study due to positive SARS-CoV-2 tests. One subject in Cohort 2B did not receive the study drug on Days 14 or 15 due to AEs of abdominal pain and metrorrhagia, but continued study for safety measures.

Within the SOC 'cardiac disorders', 2 subjects in Treatment A1 (600 mg VT-1161), 1 subject in Treatment A2 (1200 mg VT-1161) and 1 subject in Treatment B (moxifoxacin) reported AEs of palpitations. One subject in Treatment C1 (placebo) reported an AE of sinus tachycardia. Furthermore, 1 subject in Treatment A1 (600 mg VT-1161) reported syncope which is described:

Subject (b) (6) (36 y/o white female) reported palpitations on 2 occasions (following 600 mg VT-1161 and 1200 mg VT-1161). This subject also reported multiple AEs, including syncope (mild, resolved), fatigue, rhinorrhea, chest discomfort, headache, sluggishness, and indigestion, in addition to clinically significant laboratory results of elevated ALP and ALT.

Reviewer's comment: *None of the events identified to be of clinical importance or suggesting of arrhythmia per the ICH E14 guidelines (i.e., significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

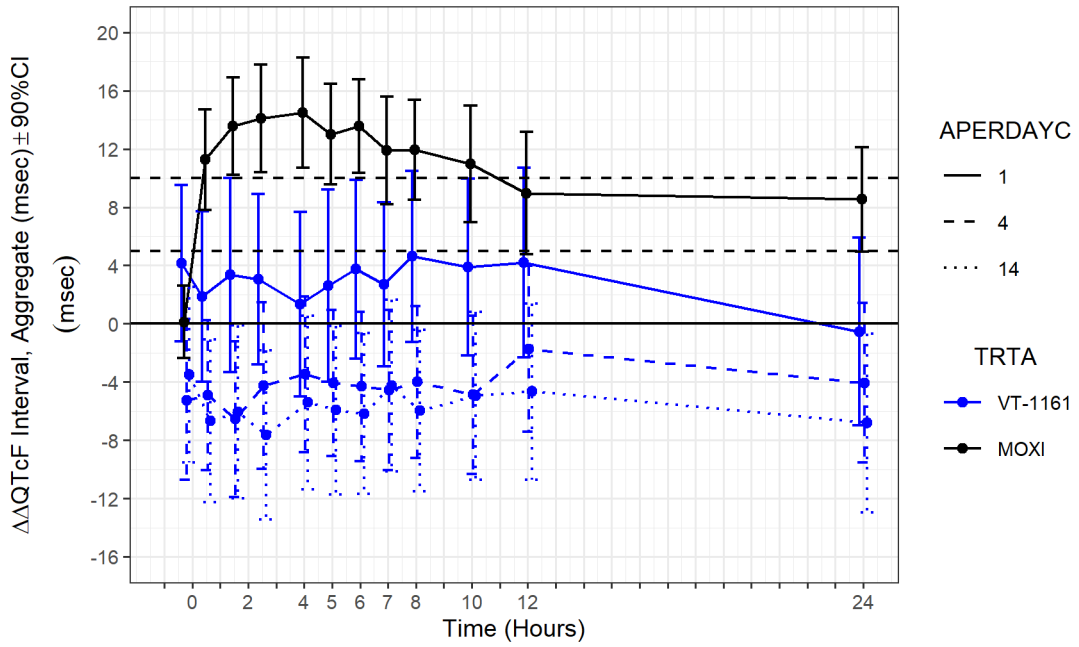


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hours)	ΔΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
VT-1161	1	28 / 15	12.0	4.2	(-2.3 to 10.7)
VT-1161	4	28 / 28	12.0	-1.7	(-7.4 to 4.0)
VT-1161	14	24 / 23	-0.2	-3.5	(-9.5 to 2.5)

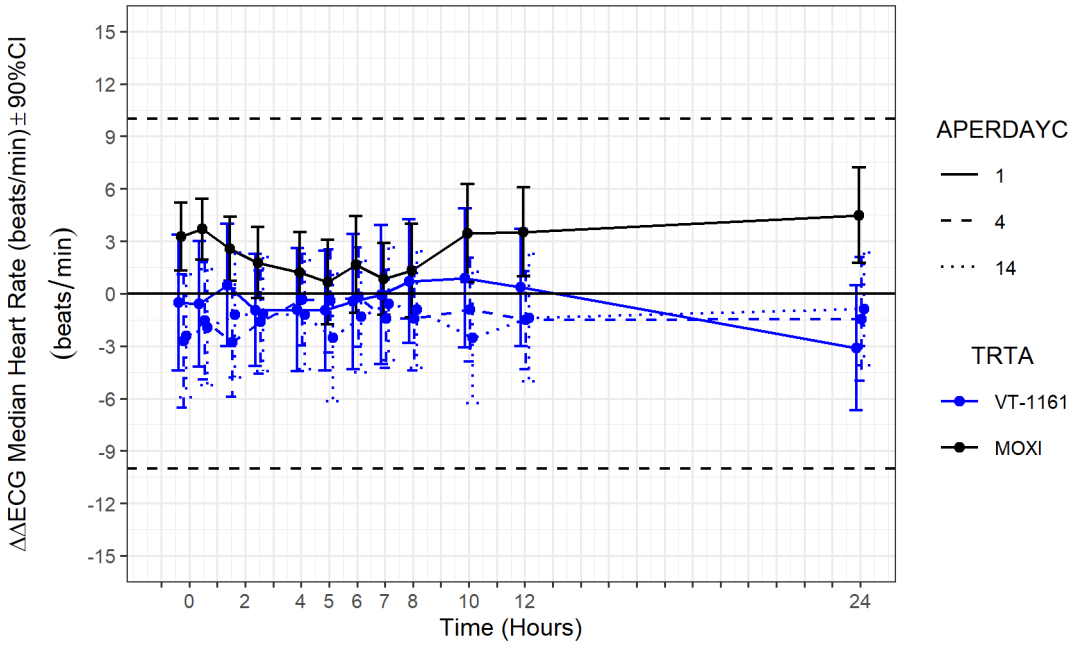
4.3.1.1 Assay Sensitivity

Assay sensitive was established using exposure-response analysis of moxifloxacin data (Section 4.5.1.).

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

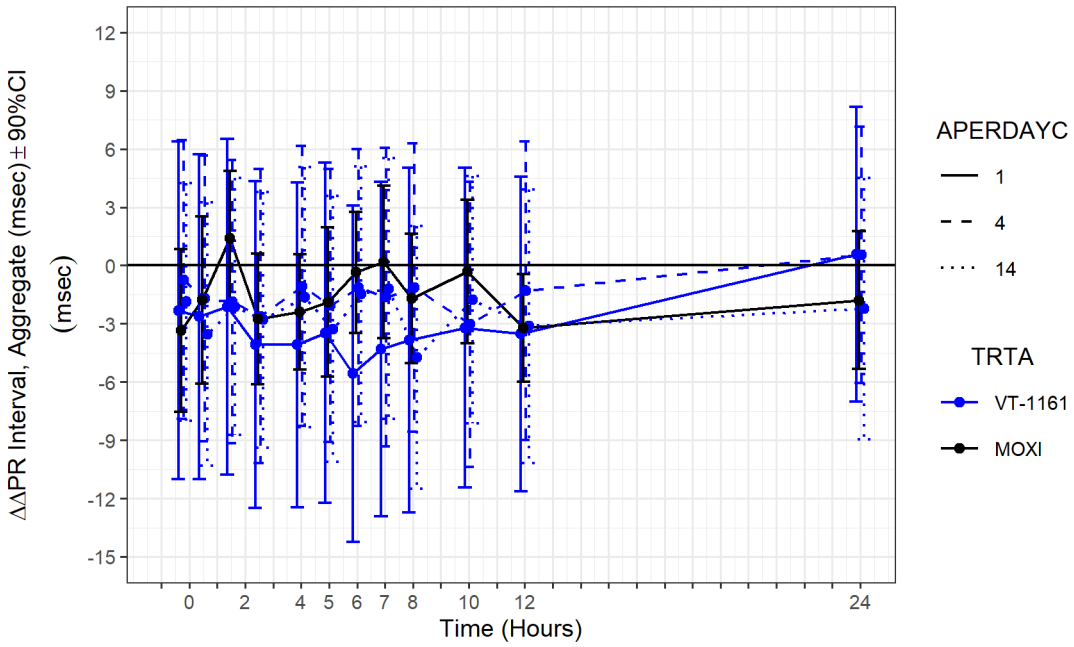
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

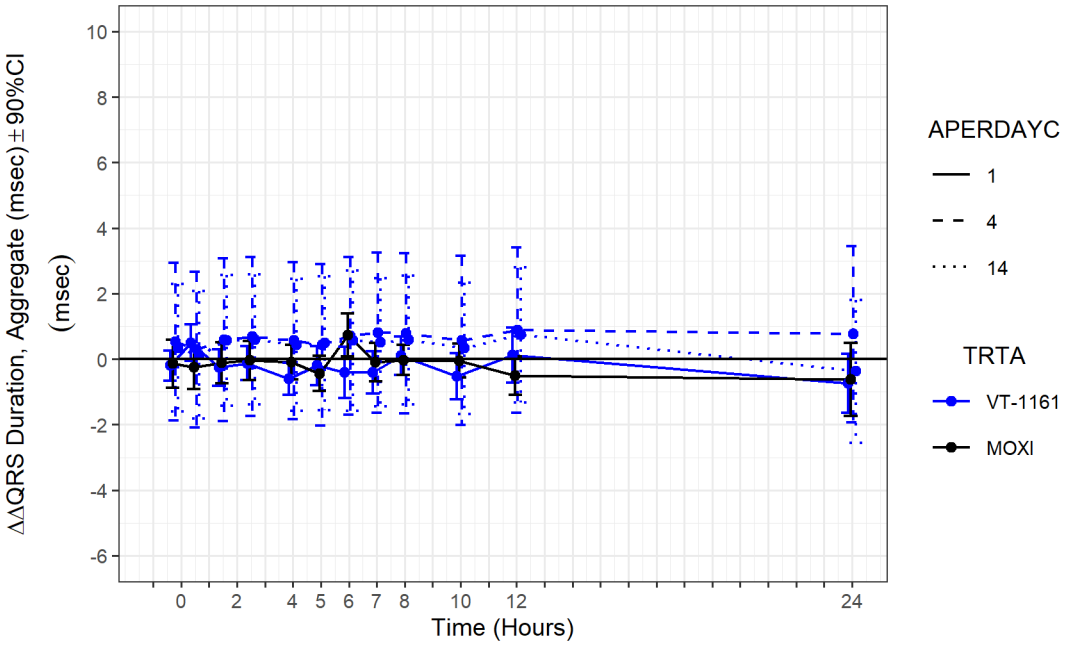
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects having observed QTcF above 450 msec or change from baseline above 60 msec after receiving VT-1161.

4.4.2 HR

None of the subjects experienced HR >100 beats/min.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

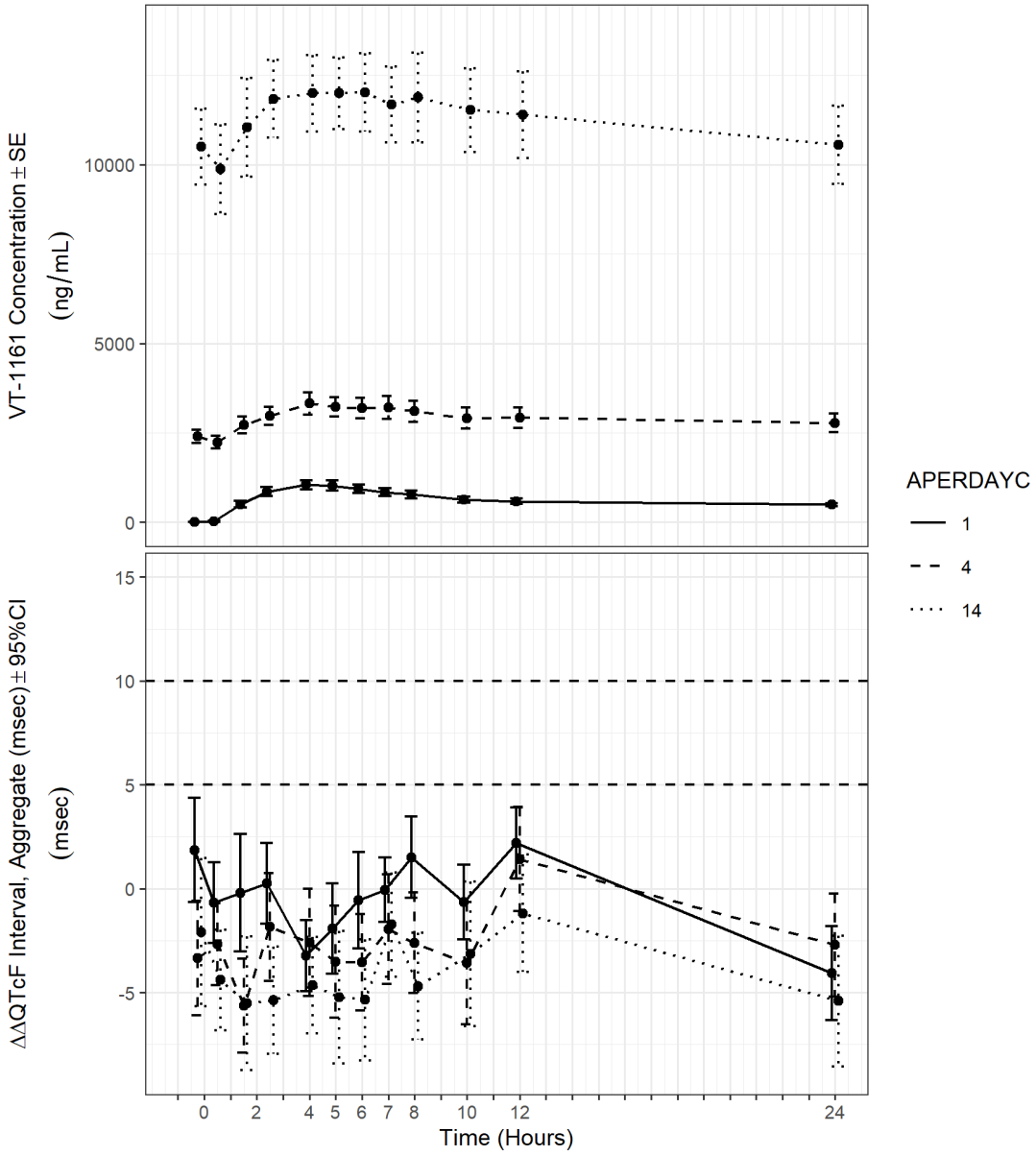
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of VT-1161 and ΔΔQTcF. Exposure-response analysis was

conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between VT-1161 concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between VT-1161 concentration and ΔQTc and 3) a non-linear relationship.

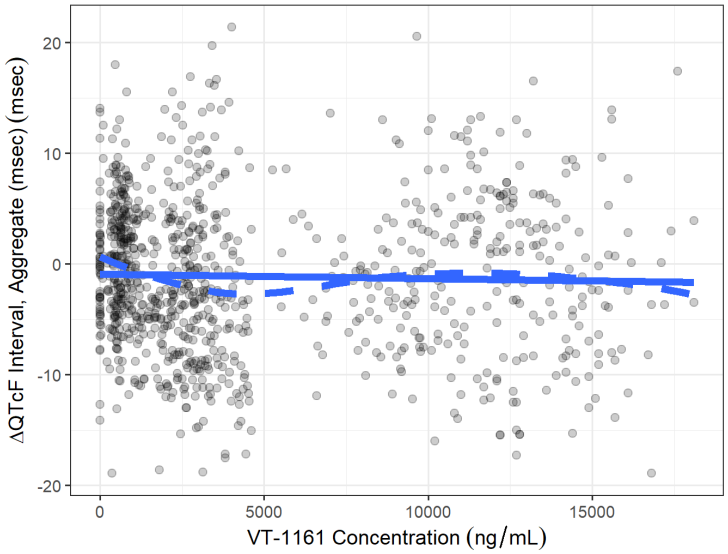
Figure 5: Time-course of VT-1161 Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

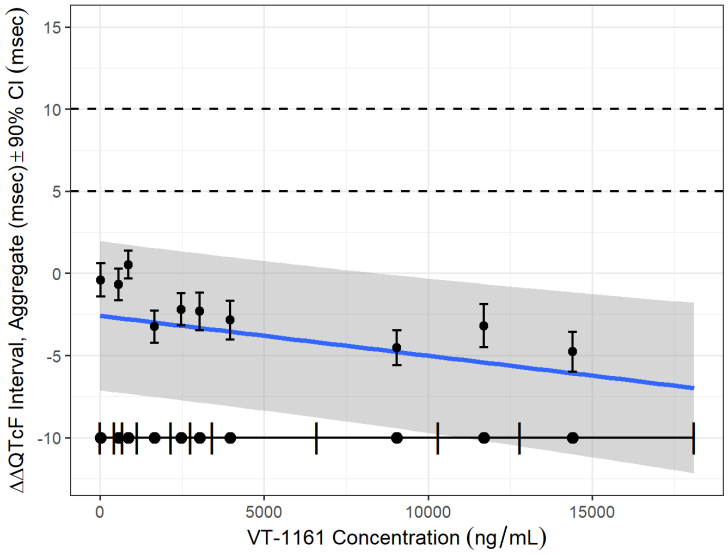
An evaluation of the time-course of VT-1161 concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of VT-1161 indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 8 bpm (Sections 4.3.2 and 4.4.2).

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between VT-1161 concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between VT-1161 concentration and ΔQTc and supports the use of a linear model.

Figure 7: Goodness-of-fit Plot for QTcF



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 3.

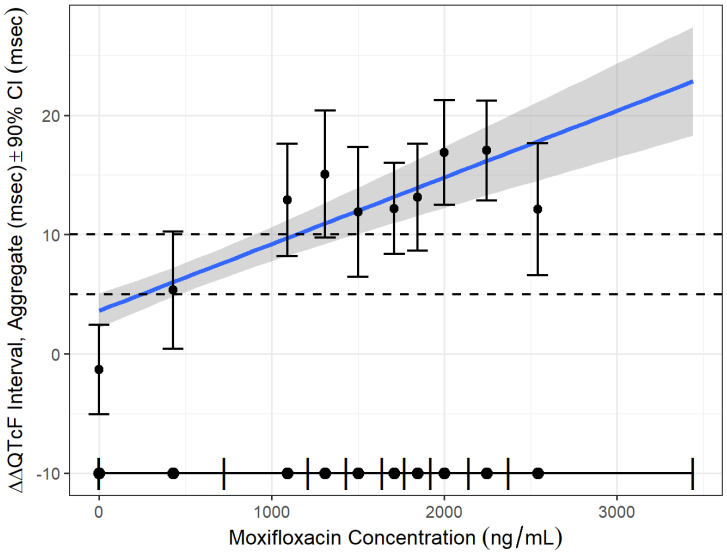
Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	VT-1161 Concentration (ng/mL)	ΔΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
T-1161	1	1059.1	-2.8	(-7.4 to 1.7)
T-1161	4	3440.5	-3.4	(-8.0 to 1.1)
T-1161	14	12597.1	-5.6	(-10.5 to -0.8)

4.5.1 Assay Sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group is generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Figure 8: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin



The goodness-of-fit plot for moxifloxacin is shown in Figure 8 and the predicted QTc at the geometric mean Cmax is listed in Table 4.

Table 4: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin Concentration (ng/mL)	ΔΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	2262.5	16.3	(13.4 to 19.2)

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health
Addendum to the November 10, 2021 Review

Date: 11/23/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Anti-Infectives (DAI)

Drug: Oteseconazole Capsule

NDA: 215888

Applicant: Mycovia Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: reduction in recurrent vulvovaginal candidiasis (RVVC) in females who are not of reproductive potential

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215888
- DAI Consult form from DPMH. DARRTS Reference ID 4833383
- Ophthalmalology Consult for Oteseconazole, NDA 215888. September 27, 2021. Wiley Chambers. DARRTS Reference ID 4863160
- DPMH Consult for Oteseconazole, NDA 215888. November 10, 2021. Wenjie Sun, MD. DARRTS Reference ID 4886476

Brief Addendum
DPMH had further discussion with DAI on November 19 and 22, 2021regarding oteseconazole labeling. Although DPMH had recommended updating the Indication and Usage section to include females who are not of reproductive potential, DAI was concerned that updating the Indication and Usage section and adding this information to subsection 8.1 and 8.2 was not enough to discourage use of oteseconazole in females of reproductive potential and in pregnant and lactating women. In addition to updating the Indication and Usage section, DAI proposed the following labeling edits:

- Contraindication for use of oteseconazole in pregnant and lactating women and in females of reproductive potential.
- a Warning and Precaution for Embryofetal Toxicity based on the ocular finding in rats in the pre-and post-natal development studies.
- The addition of information to subsection 8.3 to provide a definition of the term "females not of reproductive potential."

DAI noted that the animal study findings and the long half-life of oteseconazole (114 days; and exposure window of 1.5 years) preclude adequate mitigation of potential risks associated with oteseconazole. DPMH agrees with DAI's concerns and with their approach to oteseconazole labeling. DPMH recommends the following changes to the labeling:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
VIVJOA is indicted for the reduction in recurrent vulvovaginal candidiasis (RVVC) in females of non-reproductive potential.

CONTRAINDICATION

- Pregnant and lactating women (4), (8.1), (8.2)
- Females of Reproductive Potential (4, 8.3)

WARNINGS AND PRECAUTION

- Embryofetal toxicity: Based on animal data, may cause fetal harm. Advise females of reproductive potential of potential risk to the fetus (5.1, 8.1)

FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
VIVJOA is indicted for the reduction in recurrent vulvovaginal candidiasis (RVVC) in females who are not of reproductive potential *[see Use in Specific Populations (8.3)]*.

4 Contraindication

- Pregnant and Lactating women *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.2)]*.
- Females of Reproductive Potential *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.

5 WARNINGS and PRECAUTION

5.1 Embryofetal toxicity

VIVJOA is contraindicated in females of reproductive potential and in pregnancy. Based on animal studies, oteseconazole may cause fetal harm. Based on animal studies, oteseconazole may cause fetal harm. Ocular abnormalities were observed in the offspring of pregnant rats dosed at 7.5-mg/kg/day during organogenesis through lactation in pre and postnatal development studies. The observed ocular abnormalities included exophthalmos, opacities, and cataracts. Ocular abnormalities occurred at doses about 3.5 times of the steady state clinical exposure seen with patients being treated for recurrent infection. Advise females of reproductive potential and pregnant women of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

VIVJOA is contraindicated for use in females of reproductive potential and in pregnancy because oteseconazole may cause fetal harm when administered to a pregnant woman and because its long half-life precludes adequate mitigation of potential risks associated with this drug. In animal studies, ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons (see *Data*). This cataract finding cannot be excluded in humans. There are limited human data with use of oteseconazole in pregnant women in clinical trials; these data are insufficient to exclude a potential risk of cataracts or other eye abnormalities.

Reviewer comment: The (b) (4) *statement was omitted from Risk Summary* (b) (4)

Data

Animal Data

Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats at doses about 10 times the maximum human exposure for RVVC based on AUC comparisons. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption) but there were no malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits about 6 times the maximum human exposure for RVVC based on AUC comparisons.

Ocular abnormalities (cataracts/opacities, exophthalmos, retinal atrophy, lens degeneration, hemorrhage) were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day (about 3.5 times the recommended human dose based on AUC comparisons. There were no effects on pregnancy or parturition in these pre and postnatal studies at any dose.

8.2 Lactation

Risk Summary

VIVJOA is contraindicated for use in lactating women and females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or the effects of oteseconazole on milk production. There are no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during pregnancy; however, the clinical trial results are limited by insufficient duration of infant follow up, and routine screening eye exams may have missed the presence of cataracts. Ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons *[see Use in Specific Populations (8.1)]*. There is uncertainty as to how these animal findings relate to breastfed infants.

Reviewer comment: The (b) (4) *statement was omitted from Risk Summary* (b) (4)

8.3 Males and Females of Reproductive Potential

VIVJOA is contraindicated for use in females of reproductive potential based on animal findings *[see Use in Specific Populations (8.1)]*.

Females who are not of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g. tubal ligation, hysterectomy salpingo-oophorectomy).

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: 11/10/2021 **Date consulted:** 7/29/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Anti-Infectives (DAI)

Drug: Oteseconazole Capsule

NDA: 215888

Applicant: Mycovia Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: (b) (4)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215888
- DAI consult form for DPMH, DARRTS Reference ID 4833383
- Ophthalmology Consult for Oteseconazole, NDA 215888, September 27, 2021. Wiley Chambers, MD. DARRTS Reference ID 4863160

Consult Question:

The review team requests DPMH input on the following:

- Based on the nonclinical data, do you have any recommendations regarding the applicant's proposed wording for Section 8.1 Pregnancy and Section 8.2 Lactation?
- Based on the nonclinical data, do you have any recommendations regarding use in pregnant and/or lactating women?

INTRODUCTION AND BACKGROUND

On May 27, 2021, the applicant (Mycovia Pharmaceuticals, Inc.) submitted an original NDA for Oteseconazole Capsule, NDA 215888 (b) (4) The Division of Anti-Infectives (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on July 29, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- On September 27, 2016, Oteseconazole Capsule received Qualified Infectious Disease Product and Fast Track Designation.
- On August 16, 2017, FDA confirmed priority review.
- On May 27, 2021, the applicant submitted NDA 215888, Oteseconazole Capsule (b) (4) in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.
- On July 27, 2021, the applicant submitted the name Vivjoa, alternatively (b) (4) for proprietary name review.
- On July 29, 2021, DAI consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling.
- On August 27, 2021, FDA issued an Information Request (IR) to obtain additional follow up information, on the 11 pregnancies exposed to oteseconazole in the clinical trials which resulted in live births including the breastfeeding status for these 11 patients.
- On September 15, 2021, Mycovia Pharmaceuticals replied to the IR with a Labeling Supplement Amendment.

Drug Characteristics

Oteseconazole Characteristics[1]

Drug Class	Antifungal
Mechanism of action	(b) (4)

[1] Based on applicant proposed labeling and discussion with DAI review team. (DPMH Personal Communication with Clinical Team on 9/13/2021, Clinical Pharmacology Team on 9/13/2021).

Molecular weight	527 Daltons
Half-life	114 days
Protein Binding	>99%
Bioavailability	75-94%

Serious Adverse Reaction: none listed

PREGNANCY

Vulvovaginal Candidiasis and Pregnancy[2]

Vulvovaginal candidiasis is one of the most common causes of vulvovaginal itching and discharge. The disorder is characterized by inflammation in the setting of Candida species. Treatment is indicated for the relief of symptoms. Ten to twenty percent of females of reproductive potential who harbor Candida species are asymptomatic; these females do not require therapy.[3] Recurrent vulvovaginal candidiasis (RVVC) is defined as four or more episodes of symptomatic infection within one year.[2] Vaginal cultures should always be obtained to confirm the diagnosis and identify less common Candida species, if present. The prevalence of RVVC is difficult to assess. In an internet survey study of over 7000 females across seven countries, the estimated probability of RVVC by age 50 ranged from 14 to 28 percent, with a mean of 23 percent.[4]

The treatment of vulvovaginal candidiasis in pregnant people is primarily indicated for relief of symptoms; vaginal candidiasis is not associated with any adverse pregnancy outcomes.[2] This approach is consistent with statements from United States Centers for Disease Control and Prevention (CDC), the FDA, and others.[5,6,7,8] In pregnancy, the first line treatment is topical imidazole (clotrimazole or miconazole) vaginally for several days. Azoles are avoided during the first trimester of pregnancy because the potential for miscarriage and impact on birth defect is unclear.[2]

- A cohort study of over 3300 females who received 150 to 300 mg oral fluconazole between 7 and 22 weeks of pregnancy reported an approximately 50 percent increased risk of miscarriage in exposed people compared with either unexposed people or people

[2] Sobel, JD. Candida vulvovaginitis: Treatment. UpToDate. Accessed 8/5/2021.
[3] National guideline for the management of vulvovaginal candidiasis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). Sex Transm Infect 1999; 75 Suppl 1:S19.
[4] Blostein F, Levin-Sparenberg E, Wagner J, Foxman B. Recurrent vulvovaginal candidiasis. Ann Epidemiol 2017; 27:575.
[5] Guidelines for the Prevention and Treatment of opportunistic Infections in Adults and Adolescents with HIV. U.S Department of Health and Human Services. May 2020. https://aidsinfo.nih.gov/guidelines (Accessed on June 29, 2020).
[6] Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64:1.
[7] Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. Cochrane Database Syst Rev 2001; CD000225.
[8] US Food and Drug Administration. Safety communication: Oral fluconazole in pregnancy. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm497656 htm?source=govdelivery&utm_medium=email&utm_source=govdelivery (Accessed on April 26, 2016).

treated with vaginal azole therapy.[9]

- Oral fluconazole therapy does not appear to increase the risk of stillbirth or neonatal death.[10,11]
- Overall, the data appear reassuring for women who took low-dose fluconazole (150 mg) before realizing that they were pregnant[12], although an increased risk of cardiac and musculoskeletal anomalies cannot be definitively excluded, especially at higher doses.[10,13]

Current therapy, fluconazole 150 mg every 72 hours for three doses followed by maintenance fluconazole therapy once per week for six months, used to treat RVCC is based on expert opinion.[2] After discontinuation of the therapy, some patients achieve a prolonged remission, while up to 55 percent relapse.[14] The azoles are not recommended to be used in pregnancy.

Reviewer comment: There are no approved treatments for RVVC. The current approaches using fluconazole to treat RVCC are not approved treatments but based on expert opinion.

REVIEW
PREGNANCY
Nonclinical Experience

Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats at doses about 10 times the maximum human exposure for RVVC based on AUC comparisons. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption) but there were no malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits about 6 times the maximum human exposure for RVVC based on AUC comparisons.

Ocular abnormalities (cataracts/opacities, exophthalmos, retinal atrophy, lens degeneration, hemorrhage) were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day (about 3.5 times the recommended human dose based on AUC comparisons). There were no effects on pregnancy or parturition in these pre and postnatal studies at any dose.

The reader is referred to full Pharmacology/Toxicology report by Owen McMaster, Ph.D. and

[9] Mølgaard-Nielsen D, Svanström H, Melbye M, et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA 2016; 315:58.
[10] Bérard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. CMAJ 2019; 191:E179.
[11] Pasternak B, Wintzell V, Furu K, et al. Oral Fluconazole in Pregnancy and Risk of Stillbirth and Neonatal Death. JAMA 2018; 319:2333.
[12] Fluconazole tablet. US Food and Drug Administration (FDA) approved product information. Revised November, 2015. US National Library of Medicine. (Available online at www.dailymed nlm nih.gov (accessed January 6, 2016).
[13] 28.Zhu Y, Bateman BT, Gray KJ, et al. Oral fluconazole use in the first trimester and risk of congenital malformations: population-based cohort study. BMJ 2020; 369:m1494.
[14] 54.Collins LM, Moore R, Sobel JD. Prognosis and Long-Term Outcome of Women With Idiopathic Recurrent Vulvovaginal Candidiasis Caused by Candida albicans. J Low Genit Tract Dis 2020; 24:48.

Terry Millar, Ph. D.

Reviewer comment:
In pre- and postnatal development (PPND) rat studies, there were increased cases of ocular abnormalities, including opacity/cataracts exophthalmos, retinal atrophy, lens degeneration, hemorrhage in rat offspring administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 3.5 times the recommended human dose based on AUC comparisons. The ocular abnormalities were not evident in the rat pups immediately after birth or when the pup's eyes first opened at PND17. The ocular abnormalities were observed in rat pups on PND 21. Because the estimated half-life for oteseconazole is long, 114 days, it is unclear if the late presentation of cataracts resulted from transplacental exposure to oteseconazole during pregnancy or due to exposure via lactation.

No cataracts were reported in the embryofetal development (EFD) study in rats or rabbits. Although an increased incidence of cataracts was not observed in the EFD study in the oteseconazole exposed group, it is important to note that this finding is not unexpected. The DAI Pharmacology Toxicology team noted that based on how the animals are sacrificed and how the specimens are processed, it would be difficult to assess for cataracts in animals exposed during the EFD study.

Review of Clinical Trials

In Phase 2/3 studies, there were 20 pregnant subjects with RVVC who were exposed to oteseconazole and 9 who were exposed to placebo. The oteseconazole dosing and duration of treatment is included in Table 1 below. Additionally, there was one subject who was in the ≥300mg oteseconazole dose group. She terminated the pregnancy.

Table 1: Summary of Pregnancies- Phase 2/3 RVVC Pool[15]

	Oteseconazole							
Preferred Term	150 mg for 12 weeks N=475 n (%)	1050 mg Loading Dose N=663 n (%)	1050 mg Loading Dose (Phase 3 Studies) N=580 n (%)	600 mg on Day 1 and 450 mg on Day 2 N=146 n (%)	2100 mg Loading Dose N=83 n (%)	For 24 Weeks N=83 n (%)	Total N=746 n (%)	Placebo N=336 n (%)
Pregnancies	12 (2.5)	17 (2.6)	11 (1.9)	3 (2.1)	3 (3.6)	3 (3.6)	20 (2.7)	9 (2.7)

Abbreviations: ISS=integrated summary of safety; RVVC=recurrent vulvovaginal candidiasis
Source: Table ISS.24.4

The reader is referred to APPENDIX A for tabulated pregnancies and their outcomes in the clinical trials. The summaries of all pregnancy outcomes in all phases of the clinical trials are noted below:

- There were 24 pregnancies in 21 subjects who received oteseconazole in the clinical trials
  - 11 live births (all healthy per applicant, 1 was preterm, 3 Caesarean section (c/s) births)
  - 7 elective terminations (TABs) (Subject (b) (6) had two terminations in CL-017; reasons for termination were not provided)
  - 3 spontaneous miscarriages (SABs)

[15] Applicant's Summary of Clinical Safety for Oteseconazole, page 158.

    - one patient had a second pregnancy resulting in a healthy live birth in the trial (CL-017)
    - one has SAB after she completed 24 weeks of investigational product (IP) treatment.
    - one has a chemical pregnancy. This pregnancy failed to implant after 8 weeks of IP treatment.
- 1 ongoing pregnancy
- 2 lost to follow-up

In the applicant's response to the FDA IR, which was received on September 15, the applicant confirmed that the 11 exposed live births were only followed to birth; these infants were not followed beyond birth. However, the applicant did attempt to contact each site and noted that eight infants continue to be reported as healthy with no known congenital anomalies. Three patients did not respond to recent contact. Of the eight patients that responded, six patients breastfed their infants, one did not breastfeed her infant, and for one patient the breastfeeding status was unknown.

Review of Literature

Oteseconazole is a new molecular entity, and there are no published literature on oteseconazole use in pregnancy.

In general, oral antifungal drugs of the azole class (e.g. ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole) have been associated with teratogenic effects in animal reproduction studies (cleft palate, craniofacial ossification, wavy ribs).[16] Human studies regarding use of azoles during pregnancy have been sparse with the exception of fluconazole. Case reports of infants exposed to high dose maternal fluconazole (400-800 mg/day) during most or all of the first trimester describe a pattern of distinct congenital anomalies (brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease), which are similar to those seen in animal studies.[17]

In a Danish population-based epidemiologic study, 1079 pregnant women were prescribed fluconazole during the first trimester (797 received 150mg, 235 received 300mg and 47 received 350-600mg). There were no increases in fetal malformations, fetal loss, preterm birth or low birth weight.[18]

Recently, Mølgaard-Nielsen et al.[19] analyzed the use of oral fluconazole, itraconazole and ketoconazole during the first-trimester in all Danish pregnant women from 1996 to 2011. A total of 976,300 liveborn infants were included in the study. There were 7352 pregnancies exposed to fluconazole, 687 pregnancies exposed to itraconazole and 72 pregnancies exposed to

[16] Pilmis B, et al. Antifungal drugs during pregnancy: an updated review. J antimicrobe Chemother 2015;70: 14-22.
[17] Approved Diflucan labeling for NDA 019949. Pfizer. Drugs@FDA. Last updated 9/8/2020. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019949
[18] Nørgaard M, Pedersen L, Gislum M et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. J Antimicrob Chemother 2008; 62: 172–6.
[19] Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. New Engl J Med 2013; 369: 830–9.

ketoconazole. Cumulative doses of fluconazole included 150 mg (n=4082, 56%), 300 mg (n=2252, 31%) or 350 –600 mg (n=1018, 14%). Overall, there was no significantly increased risk of birth defects that were observed in other studies with fluconazole exposure during pregnancy; however, the risk for tetralogy of Fallot among fluconazole-exposed pregnancies was three times higher than unexposed pregnancies. In a post hoc exploratory analysis, fluconazole was not associated with a significantly increased risk of conotruncal heart defects (a subgroup that includes tetralogy of Fallot), although the adjusted prevalence odds ratio was 1.65. No significantly increased risk of birth defects was observed among itraconazole and ketoconazole exposed pregnancies. The authors noted that although fluconazole may confer an increased risk of tetralogy of Fallot, the absolute risk was small, and the association needs to be confirmed.

Reviewer comment:
Findings of cataracts in rats in the pre- and post-natal development study raise concerns for cataract development in humans. The available data on the use of oteseconazole during human pregnancy are limited to 11 exposed pregnancies that resulted in live births. At birth, none of the exposed infants had cataracts. When the applicant contacted the study sites in September 2021, there were eight reported healthy infants and three infants that were lost to follow-up. The follow up time varied from six months to almost six years after birth. Although, this is reassuring, it is limited to a small number of cases.

In a recent Ophthalmology consult,[20] the Ophthalmology Team notes "the clinical trials with this product did not report high numbers of subjects with cataracts, but the observation period of this trial was not likely long enough to evaluate cataract development. Cataract development due to drug products is often not noticed until 12-36 months after the administration of the drug product." Ophthalmology and DAI Pharmacology/Toxicology noted that the finding of cataracts in EFD or PPND studies have not been observed in any other drugs products. Oteseconazole is the first drug that has produced cataract findings in PPND studies.

This reviewer notes that the pathogenesis of neonatal cataracts is not well understood and may occur at variable time periods depending on the cause.[21] Therefore, it is unclear when the injury occurred in rats. Additionally, the 11 cases of human pregnancy exposure had variable exposure times and thus variable serum concentrations during the "sensitive period." Seven of the 11 patients received oteseconazole during the pre-pregnancy exposure window, three patients received oteseconazole during the first trimester, and one patient received oteseconazole during the 2nd and 3rd trimester.

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
It is not known if oteseconazole is present in animal milk. Ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day

[20] Ophthalmology consult review by Wiley A. Chambers, M.D. DARRTS Reference ID 4863160.
[21] Lloyd IC, et al. Neonatal cataract: Etiology, pathogenesis and management. Eye 1992;6: 184-196.

6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons.

The reader is referred to full Pharmacology/Toxicology report by Owen McMaster, Ph.D. and Terry Millar, Ph.D.

Review of Clinical Trials

In the applicant's response to FDA IR received on September 15, the applicant confirmed that the 11 exposed live births were only followed to birth and not beyond. However, the applicant did attempt to contact each site and noted that eight infants continue to be reported as healthy, and three patients did not respond to recent contact. Of the eight patients that responded, six patients breastfed their infants, 1 did not breastfeed her infant, and for one the breastfeeding status was unknown. Of the six patients who breastfed their infants, four are currently breastfeeding, and two were breastfed for a short duration (2 weeks and <3 weeks).

Review of Literature

Oteseconazole is a new molecular entity, there no published literature on oteseconazole use during lactation.

Reviewer comment:
There are no data on whether oteseconazole is present in animal milk. Because oteseconazole has a long half-life and the rats were exposed during pregnancy and lactation, it is difficult to separate the time-period. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Male rats were administered daily oral doses of 0, 0.5, 3, or 10 mg/kg/day oteseconazole beginning 42 days prior to pairing with untreated females, through the mating and post-mating period until euthanasia on Day 76 of treatment followed by a 12-week recovery period. There were no effects on reproductive and fertility parameters at the time of mating at 10 mg/kg/day (7 times the maximum human exposure for RVVC based on AUC comparisons). There were changes Increased incidences of abnormal sperm were observed at 3 mg/kg/day and sperm counts were reduced at 10 mg/kg/day. Although fertility was unaffected, sperm concentration remained reduced at the end of the recovery period.

Female rats were administered daily oral doses of 0, 1.5, 5, or 25 mg/kg/day oteseconazole beginning 28 days prior to cohabitation with untreated males, continuing throughout mating and through gestational day 7. No effects on estrous cyclicity, effects on reproductive and fertility parameters were observed at 25 mg/kg/day in the presence of maternal toxicity (11 times the maximum human exposure for RVVC based on AUC comparisons).

The reader is referred to full Pharmacology/Toxicology report by Owen McMaster, Ph.D. and Terry Millar, Ph.D.

Reviewer comment:
There is no published literature on oteseconazole and human fertility. Animal fertility studies did not show any adverse effects on fertility. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

There were 24 pregnancies exposed to oteseconazole in the clinical trials with 11 live births. Although there were no reported adverse effects, including cataracts, in any of the 11 live born infants exposed to oteseconazole in utero, the number of exposed pregnancies and the duration and quality (lack of formal examination by ophthalmologist) of follow up is insufficient.

Although cataracts were observed in rats exposed to oteseconazole during a pre- and postnatal development study, the clinical relevance of this finding is uncertain. In their review, the Ophthalmology Team noted that "relatively little is known about the development of cataracts *in utero*… Drug products which cause the development of cataracts in [non]humans sometimes also cause cataract development in humans… It is therefore not known whether the cataract findings in rats represent a risk to humans… In the absence of knowing the relevance of the finding, it is recommended that the finding be included in the package insert of the product." DPMH agrees that the animal pre- and postnatal development study findings should be described in the Animal Data section of labeling.

Additionally, the treatment of vulvovaginal candidiasis in pregnant people is primarily indicated for relief of symptoms; vaginal candidiasis has not been associated with adverse pregnancy outcomes.[2] The benefit/risk ratio in this case is to weigh the benefit of reduction of recurrent yeast infection in pregnancy, which has not been associated with adverse pregnancy outcomes, against the potential risk of neonatal cataract development based on animal studies with unknown clinical significance. DPMH discussed the animal study findings and benefit/risk analysis with the DAI Clinical Team at a meeting on November 5, 2021. DPMH is concerned that by including a Warning and Precaution for Embryofetal Toxicity and a Pregnancy Contraindication in labeling that the risk of the drug outweighs the drug's potential benefit in females of reproductive potential. Additionally, DPMH is concerned that the drug's long half-life (114 days) will make it difficult for females of reproductive potential to remain on contraception for 1.5 years and that there could be unintended pregnancies. DPMH and DAI agreed that the drug should not be indicated for use in females of reproductive potential but rather for use in females who are not of reproductive potential. Since the indicated population will include females who are not of reproductive potential, the (b) (4) statement is not applicable and will be omitted from 8.1, Risk Summary.

Since there are significant concerns with approving oteseconazole in females of reproductive potential (ie. concerning animal findings, unknown clinical relevance of cataract findings, long half-life), and since oteseconazole will be indicated for use in females who are not of reproductive potential, DPMH does not recommend a postmarking pregnancy study at this time.

Lactation

It is not known if oteseconazole is present in human or animal milk. Cataracts were observed in rats on postnatal day 21 during the pre- and postnatal developmental study at a dose that was 2

times the MRHD. The NOAEL was about 0.6 times the MRHD using AUC comparisons. In the clinical trials, there were six patients who were exposed to oteseconazole during pregnancy and went on to breastfeed their infants. Although there are no reports of any adverse infant outcomes, including cataracts, the infants were not followed for a sufficient time-period and did not have formal evaluation by an ophthalmologist. Therefore, the development of cataracts may have been missed.

Since oteseconazole will not be indicated for use in females of reproductive potential, the (b) (4) statement will not be included in subsection 8.2 of labeling. Additionally, a (b) (4) is not required (b) (4) (b) (4)

Females and Males of Reproductive Potential

There are no human data on the effects of oteseconazole on human fertility. An animal fertility study did not show any adverse effects on fertility. There is no anticipated drug-to-drug interaction between oteseconazole with hormonal contraceptives. This was confirmed in discussion with DAI Clinical Pharmacology Team.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). The labeling below has been developed in discussion with the DAI review division. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHT PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATION----------

Pregnancy: not indicated for use in females of reproductive potential (8.1)
Lactation: not indicated for use in females of reproductive potential (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

OTESECONAZOLE is not indicated for use in females of reproductive potential. In animal studies, ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons (see *Data*). This cataract finding cannot be excluded in humans. There are limited human data with use of oteseconazole in pregnant women in clinical trials; these data are insufficient to exclude a potential risk of cataracts or other eye abnormalities.

Data

Animal Data
Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats at doses about 10 times the maximum human exposure for RVVC based on AUC comparisons. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption) but there were no malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits about 6 times the maximum human exposure for RVVC based on AUC comparisons.

Ocular abnormalities (cataracts/opacities, exophthalmos, retinal atrophy, lens degeneration, hemorrhage) were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day (about 3.5 times the recommended human dose based on AUC comparisons. There were no effects on pregnancy or parturition in these pre and postnatal studies at any dose.

8.2 Lactation
Risk Summary
OTESECONAZOLE is not indicated for use in females of reproductive potential. There are no data on the presence of oteseconazole in human or animal milk or the effects of oteseconazole on milk production. There are no reported adverse effects in breastfed infants following maternal exposure to oteseconazole during pregnancy; however, the clinical trial results are limited by insufficient duration of infant follow up, and routine screening eye exams may have missed the presence of cataracts. Ocular abnormalities were observed in a pre and postnatal study in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at doses about 3.5 times the recommended human dose based on AUC comparisons *[see Use in Specific Populations (8.1)]*. There is uncertainty as to how these animal findings relate to breastfed infants.

APPENDIX A. Pregnancy outcomes in clinical trials

Table 1. Pregnancy Listing - Phase 2/3 RVVC Pool[22]

Subject ID	Study	OTE or Placebo	Estimated Due Date	Birth Outcome (If Applicable)	Timing (weeks)	Congenital Anomaly (9/2021)	Breastfeeding
(b) (6)	CL-011	Placebo	(b) (6)	Healthy, live birth			
	CL-011	OTE		Healthy, live birth	Pre-pregnancy (-14^{-4} to -2^{-6} weeks) Pre-14 days to 2 weeks pre -pregnancy	Unknown	Unknown
	CL-011	OTE		Healthy, live birth; C-section	Pre-pregnancy and 1st trimester	None	Yes (<3 weeks)
	CL-011	Placebo		Not reported			
	CL-012	OTE		Not reported	1st trimester		
	CL-012	Placebo		Healthy, live birth			
	CL-012	OTE		Healthy, live birth	Pre-pregnancy (-31^{-6} to -20^{+0} weeks)	None	Yes (11 months and ongoing)
	CL-012	OTE		Healthy, live birth; C-section	Pre-pregnancy (-19^{-1} to -7^{-2} weeks)	None	Yes (10 months and ongoing)
	CL-012	Placebo		Healthy, live birth; C-section			
	CL-012	Placebo		Elective termination			
	CL-012	OTE		Not reported	Pre-pregnancy (-23^{+3} to 16^{+1} weeks)		
	CL-012	OTE		Healthy, live birth	Pre-pregnancy (-44^{+3} to -32^{+3} weeks)	None	Yes (6 months and ongoing)

[22] Modified from Applicant's Table 39. Pregnancy Listing-Phase 2/3 RVVC Pool, page 159 from applicant's submission titled "Summary of Clinical Safety." The added EDC was based on the applicant's submitted study report. Timing was calculated based on the EDC.

(b) (6)			(b) (6)				
	CL-012	OTE		Not reported	Pre-pregnancy (-44^{+6} to -30^{+6} weeks)		
	CL-017	OTE		Elective termination	Pre-pregnancy (-16^{+4} to -4^{+4} days)		
	CL-017	OTE		Elective termination	Pre-pregnancy (-38+3 to -26+3 weeks)		
	CL-017	OTE		Spontaneous abortion	Pre-pregnancy (-10^{+1} to 1^{+6} weeks)		
	CL-017	OTE		Healthy, live birth; C-section	Pre-pregnancy (-29^{+4} to -17^{+4} weeks)	None	No
	CL-017	Placebo		Healthy, live birth; C-section			
	CL-017	OTE		Healthy, live birth	Pre-pregnancy (-32^{-2} to -20^{+2} weeks)	None	Yes (6 months and ongoing)
	CL-006	OTE		Elective termination	Pre-pregnancy and 1st		
	CL-006	OTE		Elective termination	Pre-pregnancy and 1st		
	CL-006	OTE		Healthy, live birth	2nd and 3rd trimester	Unknown	Unknown
	CL-006	OTE		Elective termination	Pre-pregnancy (-41^{-1} to -17^{-2} weeks)		
	CL-006	OTE		Healthy, live birth	Pre-pregnancy (-24^{-5} weeks to -6 days)	Unknown/Healthy and no CA as of June 2018 (5 months of age)	Unknown
	CL-006	OTE		Healthy, live birth	Pre-pregnancy and 1st trimester	Unknown	Unknown
	CL-006	OTE		Spontaneous abortion	Pre-pregnancy (-38^{-3} to -14^{-4} weeks)		
	CL-006	OTE		Healthy, live birth	Pre-pregnancy and 1st trimester	None	Yes (2 weeks)

(b) (6)	CL-006	OTE	Unknown↓	Elective termination	Pre-pregnancy and 1st trimester		
	CL-006	OTE	Unknown**	Chemical pregnancy	Pre-pregnancy and 1st trimester		
	CL-006	Placebo		Chemical pregnancy			
	CL-006	Placebo		Healthy, live birth			
	CL-006	Placebo		Healthy, live birth			

Abbreviations: IP=investigational product; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis a. Date of positive pregnancy test or start of last menstrual period.
Source: Patient Safety Database
† calculated based on ultrasound at 5 weeks. Her LMP on the narrative is (b) (6) appears to be in error.
†† Although her EDC was unknow, her positive UPT was on (b) (6)
*EDC populated from Applicant submitted case narrative by the reviewer.
↓ EDC was not determine, date of positive UPT was (b) (6). Serum HCG was not done. Ultrasound was not reported. The subject terminated the pregnancy on (b) (6) and (b) (6) by taking mifepristone. Her LMP was (b) (6)
**EDC not determined, patient presented with positive urine and serum beta HCG tests on 8/19/2015 and then 12 days later it became negative. She received test drug on (b) (6)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENJIE SUN
11/10/2021 07:28:28 AM

MIRIAM C DINATALE
11/10/2021 08:12:00 AM

LYNNE P YAO
11/10/2021 08:16:03 AM

Medical Officer's Consultation Review of NDA 215888
Ophthalmology

NDA 215888		Submitted date:	September 3, 2021
IND 111675		Review completed:	September 27, 2021

Product Name: Vivjoa (oteseconazole) capsule

Sponsor: Mycovia Pharmaceuticals, Inc.

Therapeutic Class: Anti-fungal

Indication: [redacted] (b) (4) recurrent vulvovaginal candidiasis

Request: On May 27, 2021, a new drug application was submitted for oteseconazole for [redacted] (b) (4) [redacted] (b) (4) recurrent vulvovaginal candidiasis.
EDR Location: \\CDSESUB1\evsprod\NDA215888\0001

We are requesting recommendations from the Division of Ophthalmology concerning non-clinical ocular findings (i.e., opacities/cataracts and exophthalmos) exhibited across several strains of rat pups in pre- and post-natal studies, a summary of which is found below. We also obtained consultation from Dr. Lori Kotch, who provided a response on 26 August 2021, and the from the Division of Pediatric and Maternal Health.

In Pre- Post-natal study 12344001, oteseconazole was orally administered to pregnant SD rats at 0, 1, 3 and 7.5 mg/kg/day once daily from Gestation Day 6 through Lactation Day 20 resulted in eye opacities at doses as low as 3 mg/kg. As early as Day 21 (but not on Day 17), opacities were observed during clinical evaluations. Some animals developed cataracts/opacities later in the observation period beginning on Days 49, 56 or 84. The development of these opacities/cataracts was confirmed in three subsequent studies (#1234002, 1234003 and 1234004), in which only the 7.5 mg/kg dose was used. Ocular examinations were conducted by a board-certified veterinary ophthalmologist in both pre-weaned and weaned rat pups (generally PND 17–22 and PND 30–36) using an indirect ophthalmoscope and slit lamp biomicroscope.

• Assuming clinical exposure of 85,000 ng·hr/mL (AUC over the proposed 11 week period), the exposure at the NOAEL (1 mg/kg associated with an AUC of 39,360 ng*hr/mL) was about 0.5 times the clinical exposure for patients being treated for the proposed indication of reduction in recurrent episodes of vulvovaginal candidiasis. Oteseconazole exposure in humans for acute VVC is estimated to be 48,000 ng·hr/mL which is similar to the exposure at the NOAEL.

Table 1: Eye findings from Pre- Post-natal study 12344001

Animal ID	Study Phase	Sex	Group	Clinical signs	Finding noted on PND	Subgroup
4040-12	Main	F	4	exophthalmos left eye	21 and 28-108	Selected for F_1 Generation; Euthanized on PND 108
				opacity left eye	49-108	
4090-03	Main	F	4	exophthalmos left eye	21	Euthanized on PND 21
4114-08	Main	F	4	exophthalmos left eye	21	Selected for F_1 Generation; Euthanized on PND 95
				opacity left eye	84	
				partial closure left eye	49-91	
4114-09	Main	F	4	exophthalmos right eye	21	Euthanized on PND 21
4075-10	Main	M	4	exophthalmos left eye	21	Euthanized on PND 21
4090-01	Main	M	4	exophthalmos right eye	21 and 25-91	Selected for F_1 Generation; ; Euthanized on PND 95
				opacity right eye	56-91	
4080-16	TK	F	4	partial closure right eye	21	Selected for F_1 Generation; Euthanized on PND 120
				red discharge right eye	21, 42, and 49	
				enophthalmos right eye	PND 35	
4096-11	TK	F	4	exophthalmos left eye	PND 21	Euthanized on PND 21
4115-08	TK	F	3	Bilateral opacity	PND 21	Euthanized on PND 21

M = Males, F = Females, PND = Postnatal Day

In Pre-postnatal study #1234004, 7.5 mg/kg oteseconazole was administered to two strains of rats, (Sprague Dawley (SD) and Wistar Han (HAN)). A high incidence of lens opacities/cataracts was observed in the 7.5 mg/kg/day groups during the preweaning evaluation on PND 17–22, (11 and 32 pups for SD and HAN, respectively) which were seen for only a single female in the SD control group and not seen in the HAN control group. The higher incidence of lens cataract was also observed at PND 30–36 (30 and 27 animals for SD and HAN, respectively) when compared to the respective control groups (7 and 0 for SD and HAN, respectively). No cataracts or opacities were reported during the embryo-fetal development study of oteseconazole but sectioning methods (i.e., Bouins fixation, razor sectioning) preclude cataract determination. Skeletal processing methods remove/macerate all soft tissues and examination of ocular tissues is not possible in fetuses assigned to skeletal exam.

Please comment on the following:

- The potential impact on pregnant and/or lactating women and their infants and your recommendations on the need for PMRs and/or registries.

- The need for additional studies or examinations to evaluate the risk(s) of exposure to oteseconazole in treated women and their offspring. If so, what study design or additional ocular findings merit further evaluation (e.g., vision and visual acuity testing, etc.)?

- Please provide any labeling recommendations and precautionary language to include in the prescribing information based on the pre-clinical findings and the implications to women of childbearing potential, pregnant and lactating women, and their infants.

Reviewer's Comments: *Comments and recommendations in this review are limited to areas of ophthalmologic concern.*

Summary from Application:
Ocular abnormalities (e.g., exophthalmos, discoloration, opacity) were observed in male and female F1 pups at 7.5 mg/kg/day in the definitive pre- and postnatal development study in rats. Although the incidence of the eye findings was low, given the eye findings were not observed in the control group a series of targeted pre- and postnatal development studies in pregnant Crl:CD®(SD) Sprague Dawley, Envigo Hsd:SD Sprague Dawley and Crl:WI(Han) rats were conducted to further evaluate and characterize potential effects on postnatal ocular development in the rat. F0 females were dosed at 0 or 7.5 mg/kg/day of oteseconazole from GD 6 through LD 20 using the same batch of oteseconazole and following the same maternal procedures as in the initial pre- and postnatal development study. Additional assessments in F1 pups during the preweaning and postweaning periods included detailed ophthalmic examinations using indirect ophthalmoscope and slit lamp biomicroscope, clinical pathology evaluation, gross necropsy and targeted tissue collection for histopathology including the eye and optic nerves.

There was an increase incidence in postweaning mortality in male and female pups at 7.5 mg/kg/day associated with animal identification procedures in Crl:CD®(SD) Sprague Dawley F1 pups (e.g., microchip implantation). The cause of death for these animals was due to excessive hemorrhage at the microchip implantation site. In general, pup mortality occurred within 24 hours of the microchip implantation such that animals which remained on study past this period survived and appeared otherwise normal until their scheduled necropsy. Correlative changes in clinical pathology parameters suggestive of coagulopathy included decreases in red cell mass (erythrocytes, hemoglobin and hematocrit), reduced erythrocyte volume and hemoglobin content (MCV, MCHC), increased platelet counts and prolongation of coagulation time (prothrombin time [PT], activated partial thromboplastin time [APTT]). Additionally, there was an increased inflammatory response (GLOB, albumin, monocytes, large unstained cells, fibrinogen). All of the above findings resolved by the terminal necropsy on PND 32-35 or PND 61-61 consistent with low or undetectable oteseconazole plasma concentrations at these intervals. Notably, a similar clinical pathology profile was observed in Hsd:SD Sprague Dawley or Crl:WI(Han) F1 rat pups in the absence of mortality, ophthalmology or anatomic pathology correlates of coagulopathy.

An increased incidence of exophthalmos, discoloration and/or opacity was observed in Crl:CD®(SD) Sprague Dawley F1 rats at 7.5 mg/kg/day starting at PND 21 which persisted until the terminal necropsy. Ophthalmology, gross and histopathological findings in the eyes of animals with exophthalmos included red discoloration, enlargement, opacity, and intraocular hemorrhage (e.g., hyphema) which correlated with clinical pathology changes consistent with coagulopathy. Similar findings were not observed in either Hsd:SD Sprague Dawley or Crl:WI(Han) F1 rat pups. Lenticular opacities (e.g., cataract), were seen in all rat strains evaluated but presentation (type and incidence) was strain-dependent. Anterior cortical cataract and nuclear cataract were most prominent in the Crl:CD®(SD) Sprague Dawley rat while nuclear cataract was most commonly observed in the Hsd:SD Sprague Dawley rat. Equatorial and nuclear cataract were most commonly observed in the Crl:WI(Han) rat. There was a lack of histopathological findings in the eyes and optic nerve as well as the Harderian gland in Crl:CD®(SD) Sprague Dawley F1 rat pups evaluated on PND 7. The absence of findings from this histopathological assessment associated with high

oteseconazole plasma concentrations in young pups suggests that structural changes to the lens likely occurs during the postnatal period and that gestational exposure (e.g., in utero) might not have played a role in development of ocular abnormalities in developing rat pups exposed to oteseconazole following maternal administration. Oteseconazole concentrations on PND 4 and 20 in Hsd:SD and Crl:WI(Han) rats were higher than those observed in Crl:CD(SD) rats. Key findings in F1 pups at 7.5 mg/kg/day from a series of investigational pre- and postnatal development studies can be generally separated into two categories: 1) ophthalmology findings generally limited to the lens and 2) a broader pattern of ophthalmology findings and mortality considered secondary to coagulopathy specific to the Crl:CD®(SD) Sprague Dawley rat. Results from these studies provide compelling evidence that the mortality and pattern of ocular abnormalities (e.g., hyphema, glaucoma, buphthalmos, optic nerve atrophy) observed in Crl:CD®(SD) Sprague Dawley rats were secondary to a species- and strain-specific coagulopathy. This is supported by a lack of similar findings in Hsd:SD and Crl:WI(Han) rats.

Lenticular opacities (e.g., cataract), were seen in all rat strains evaluated but presentation (type and incidence) was strain-dependent (refer to Tabulated Summary 2.6.7.16). Anterior cortical cataract and nuclear cataract were most prominent in the Crl:CD®(SD) Sprague Dawley rat while nuclear cataract was most commonly observed in the Hsd:SD Sprague Dawley rat. Equatorial and nuclear cataract were most commonly observed in the Crl:WI(Han) rat. These data are summarized below.

Summary of Preweaning and Postweaning Cataract Incidence Rates in F_1 Rat Pups

Study No.	Rat Strain	Incidence of Cataract[a]	
		Preweaning	Postweaning
01234002[b]	Crl:CD®(SD) Sprague Dawley	Unilateral: 8/209 (4%)	Unilateral: 12/200 (6%) Bilateral: 7/200
01234003[c]	Crl:CD®(SD) Sprague Dawley	Anterior cortical: 37/132 (28%) Nuclear: 10/132 (8%)	Anterior cortical: 9/67 (13%) Nuclear: 10/67 (15%)
01234004[d]	Hsd:SD Sprague Dawley	Nuclear: 11/65 (17%)	Nuclear: 31/65 (48%)
01234004[d]	Crl:WI(Han)	Equatorial: 28/61 (46%) Nuclear: 3/61 (5%)	Equatorial: 0/60 (0%) Nuclear: 24/60 (40%)

Ophthalmic examinations were conducted by a board-certified veterinary ophthalmologist using an indirect ophthalmoscope and slit lamp biomicroscope. Prior to examination, animals were treated with a mydriatic agent.
[a] No. Affected/No. pups examined
[b] Preweaning examination conducted on PND 15-18; postweaning examination conducted on PND 24-26 and PND 50-55
[c] Preweaning examination conducted on PND 19-20; postweaning examination conducted on PND 32-35
[d] Preweaning examination conducted on PND 17-21; postweaning examination conducted on PND 30-35

Although similar ophthalmology findings observed at 7.5 mg/kg/day reported above were not generally observed in control animals, several groups have reported incidence rates of spontaneous ocular findings in 3- to 7-week old (PND 21-PND 49) Sprague Dawley rats assessed by detailed ophthalmologic examination as part of pre-test general toxicology screens (Kuno et al., 1991, Taradach et al., 1981, Morita et al., 2020, Ban et al., 2008). The incidence rate of spontaneous ocular lesions in the lens of these rat pups (cataract: 1-40%) generally exceeded that associated with oteseconazole exposure in F1 pups at 7.5 mg/kg/day. These external historical data are considered useful in characterizing ocular abnormalities in developing Sprague Dawley pups and serves as a quality control tool for establishing the reasonableness of the spontaneous eye findings in rat pups of similar age and strain.

A unique spectrum of ocular abnormalities secondary to coagulopathy was observed in Crl:CD®(SD) Sprague Dawley F1 pups ([redacted] Study Nos. 01234002 and 01234003). Ocular findings in these animals included dark red discoloration of the eye, opacity, enlargement, hyphema, glaucoma and histopathology observations of adhesion, retinal atrophy, lens degeneration, retinal dysplasia, inflammation, hemorrhage, corneal keratinization, and optic nerve atrophy; all of which correlated with clinical pathology changes consistent with coagulopathy.

Although the underlying etiology is unclear, there may be an alteration in physiologic vitamin K and/or iron levels (or other factor related to coagulation or hemostasis) associated with the transition from milk to chow that occurs in pups of this age (Endo et al., 2011, Hegde et al., 2011). Rats are reported to have physiological anemia during the postnatal period given the relative immaturity of the hematopoietic system as well as rat milk being a poor source of iron and vitamin content (Papworth and Clubb 1995, Endo et al., 2011). Iron and vitamin K are essential for hemostasis and, in particular, the intrinsic and extrinsic clotting cascade; decreased availability or antagonism of these constituents may result in prolonged clotting times and hemorrhage. For all tested rat strains, changes in hematology and coagulation parameters in F1 pups at 7.5 mg/kg/day suggestive of coagulopathy were most prominent at weaning (PND 21), an apparent exacerbation of the background anemia and impairment of the hemostatic system. However, the coagulopathy phenotype (e.g., hemorrhagic findings) was only observed in Crl:CD®(SD) Sprague Dawley F1 pups, but not in Hsd:SD or Crl:WI(Han) rat pups. Additionally, data in adult rats also indicate a strain-dependent susceptibility to oteseconazole induced coagulopathy. For example, in the 26-week repeat dose toxicology study conducted in Crl:CD®(SD) rats ([redacted] Study No. 2130-002) the resulting change in clinical pathology profile observed was not unlike that observed in [redacted] Study Nos. 01234002 and 01234003, yet much more subtle (e.g., decreases in red cell mass, reduced erythrocyte volume and hemoglobin content, increased platelet counts, prolongation of coagulation time). Additionally, multiorgan hemorrhage was observed in high dose male Crl:CD®(SD) rats in the 104-week carcinogenicity study ([redacted] Study No. 2130-018, Section 4.2). In contrast, there were no remarkable effects on hematology or coagulation parameters nor were there anatomic pathology findings suggestive of coagulopathy in Hsd:SD rats administered oteseconazole for up to 28-days at steady-state exposures which exceed those achieved in the Crl:CD®(SD) rats (Cmax: 115,150 ng/mL; AUC0-24 = 2,117,150 ng·hr/mL). Additionally, there was a lack of remarkable changes in clinical pathology parameters and/or anatomic pathology findings suggestive of coagulopathy following chronic exposure in adult mice ([redacted] Study No. 2130-025, Section 4.1) and dogs ([redacted] Study No. 2130-001, Section 2.3.3).

Ophthalmology Reviewer's Comments and Conclusions:
Relatively little is known about the development of cataracts *in utero*. One of the more well-known products to produce cataracts in the off-spring of pregnant rats is galactose. The administration of 30% galactose in pregnant rats will cause congenital cataracts in their off-spring, and aldose reductase inhibitors (ARI) have been known to prevent these cataracts. Unfortunately, this example does not extend to humans.

Drug products which cause the development of cataracts in humans sometimes also cause cataract development in humans. Because the likelihood of developing cataracts in humans is increased in drug products which cause cataracts in nonhumans, it is often recommended that clinical trials monitor for the potential development of cataracts. There have not been enough products which cause congenital cataracts to know whether this should be recommended with drug products that cause congenital cataracts. The clinical trials with this product did not report high numbers of subjects with cataracts, but the observation period of this trial was not likely long enough to evaluate cataract development. Cataract development due to drug products is often not noticed until 12-36 months after the administration of the drug product.

It is therefore not known whether the cataract findings in rats represent a risk to humans. In the absence of knowing the relevance of the finding, it is recommended that the finding be included in the package insert of the product.

The likelihood of distinguishing the etiology of any cataract development in oteseconazole treated women or their offspring is very low. Additional studies in the oteseconazole treated women and their offspring is not recommended. To collect information on children born to mothers who have taken oteseconazole, the establishment of a registry of pregnant women who have taken oteseconazole should be considered.

As one of the only drug products which has been known to reduce the incidence of congenital cataracts in rats, consideration should be given to adding aldose reductase inhibitor treatment to the rat studies which produced congenital cataracts in off-spring rats.

The applicant has proposed the following labeling statements. It is recommended that the marked up changes be made to this proposed labeling:

Risk Summary

(b) (4)

Data

Animal Data

Rat and rabbit embryofetal development was assessed after oral administration of oteseconazole. There was no embryofetal toxicity or malformations at (b) (4) mg/kg/day following administration of oteseconazole

during organogenesis in pregnant rabbits (b) (4) times the maximum human exposure for RVVC based on AUC comparisons.

(b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of oteseconazole in (b) (4)

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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